EXHIBIT B

NICOLETTE SIGRID HORBACH, M.D.

EXPERT GENERAL REPORT

EDUCATIONAL BACKGROUND AND EXPERT QUALIFICATIONS

After graduating from Wellesley College, I attended Washington University School of Medicine in St. Louis, Missouri and completed an internship and residency in Obstetrics and Gynecology at the University of California, San Francisco followed by a fellowship in Gynecologic Urology, Laser, and Pelvic Surgery at the University of California, Irvine. For the first 10 years of my medical career, I served as a full-time university faculty member, initially at the University of California, San Francisco and later, as a tenured Associate Professor and Director of the Division of Gynecology at George Washington University Medical Center. I joined Mid-Atlantic Pelvic Surgery Associates in 1996, which became Mid-Atlantic Urogynecology and Pelvic Surgery in 2013. I am ABOG certified in Obstetric and Gynecology and ABOG/ABU subspecialty certified in Female Pelvic Medicine and Reconstructive Pelvic Surgery (FPMRS).

As a clinician, educator and national pioneer in the field of FPMRS for nearly 30 years I have served as a member of American Urogynecologic Society (AUGS) Executive Committee for over a decade and was elected President of AUGS in 1999. Appointed by the ABOG as a founding member of the American Board of Obstetrics and Gynecology (ABOG) Committee on FPMRS, I drafted the national educational requirements for fellowship training in FPMRS. From 2004–2007, I chaired the joint ABOG/ABU FPMRS Committee responsible for accrediting fellowship-training

programs and served as a member of the ABOG Board of Directors. I have worked extensively with the American College of Obstetricians Gynecologists (ACOG) authoring the Technical Bulletin on Urinary Incontinence, Precis and Prologue, and directing post-graduate educational courses in FPMRS for practicing primary care physicians and obstetrician/gynecologists. As a national spokesperson for FPMRS, I have testified before Congress and HICFA, participated in NIH Consensus Conferences to define areas of needed research, and served as an NIH study reviewer for the Pelvic Floor Treatment Network grant applications. I have authored a textbook, multiple book chapters and research papers, as well as participated in multi-centered clinical treatment trials for incontinence and prolapse. As an expert in FPMRS I have been quoted in national magazines including Glamour, Prevention, YM, Women's Health, and Cosmo and recognized nationally as a top doctor for women's health by Good Housekeeping Magazine and U.S. News and World Report.

In addition to my educational activities on the national front, throughout my entire career I have been clinical educator of medical students, residents, and fellows, interacting with them daily in the outpatient clinic, the hospital setting, and the operating room. At present I am a Clinical Professor of Obstetrics and Gynecology at George Washington University and faculty member of the National Capital Consortium Fellowship in FPMRS at the Inova Medical Center site. My commitment to medical education has been recognized by my receipt of four faculty teaching awards including the national CREOG Teaching Award for excellence in resident education.

Currently, I manage a busy urogynecologic clinical practice focused on caring for women with urinary incontinence, pelvic organ prolapse, recurrent urinary tract infections, bladder and pelvic pain, voiding dysfunction, defecatory dysfunction and fecal incontinence, dyspareunia, and the evaluation and management of complex post-operative complications following gynecologic and urologic surgeries. In my nearly 30 years in clinical practice I have seen 1,500–2,000 patients per year and have performed thousands of pelvic floor operations including open abdominal, laparoscopic, vaginal, and minimally invasive procedures. I have extensive experience with native tissue repairs, biologic grafts (autografts, allografts, and xenografts) and a wide range of monofilament and multifilament synthetic mesh materials including polypropylene, polytetrafluoroethylene, polyester, and polyethylene grafts. I have performed over 1000 mid-urethral sling procedures using various products including Ethicon's TVT and TVT-O. As a tertiary referral practice I often evaluate and treat women with complicated urogynecologic disorders who have failed prior surgical procedures and/or developed significant complications from their prior treatment including persistent and/or recurrent incontinence, infections, vaginal scarring, sexual dysfunction, chronic pelvic pain, voiding difficulties, and reactions to allografts, xenografts, and synthetic mesh materials. For more information, please see my attached CV and the list of materials I have reviewed in preparation of this report. In formulating my opinions and expert report, I relied on my education, my knowledge and review of the medical literature, my training, and my extensive clinical and surgical experience gained

over nearly 30 years of patient care. All of my opinions are stated within a reasonable degree of medical certainty.

I am being compensated $500 per hour for my work in this case. In the previous four years, I have testified as an expert at trial or by deposition in one Ethicon MUS case—Corbet v. Ethicon.

OPINIONS:

EPIDEMIOLOGY OF STRESS INCONTINENCE AND QOL IMPACT

Urinary incontinence is defined as the involuntary loss of urine due to multiple factors that affect the normal neuromuscular function of the lower genital urinary tract. Epidemiologic studies have estimated the prevalence of any urinary incontinence in community dwelling women to be 9–72%, while other studies report urinary leakage in 30–60% in middle-aged and older women. Estimates of the prevalence incontinence are limited by inconsistent methods of measurement between epidemiologic studies in different populations and by underlying differences in the age and ethnicity of study populations. The prevalence of incontinence increases with age. In a large representative United States survey of non-pregnant women, moderate or severe urinary incontinence (at least weekly or monthly leakage of more than just drops) was reported to affect 7% of women ages 20 to 39, 17% ages 40 to 59 and 23% ages 60 to 70.

Stress urinary incontinence (SUI) is the symptom of involuntary loss of urine during physical exertion such as sneezing, coughing, or exercise. The diagnosis of

stress incontinence is confirmed by the observation of urine leakage from the urethra during exertion. Stress incontinence is the most common type of leakage in community dwelling women. A review of 15 studies including over 30,000 women found 49% (range 24–75%) reported stress incontinence with 3–17% experiencing severe incontinence. While it is a common myth that incontinence is seen in only older women, in one survey the prevalence of any urinary incontinence in nulligravid young women (aged 16 to 30 years) was 12.6% with stress urinary incontinence reported even by young athletes.

Risk factors for stress incontinence include increasing age, Caucasian race, vaginal childbirth, prior pelvic surgery, menopause, obesity, and smoking. The data regarding the role of prior hysterectomy is conflicting. Urinary incontinence has been reported in 31–60% of pregnant women. While stress incontinence may resolve postpartum in some women, others, especially women >age 30 at the time of first vaginal delivery may continue to experience troublesome symptoms that may impact their ability to care for their children and participate in physical activities or exercise. Stress incontinence is known to have a major impact on quality of life affecting self-image, self-confidence, activities, and sexual relations. Given that few effective nonsurgical treatment options exist, and most women undergo surgical treatment of stress incontinence after waiting to complete childbearing, these women will often suffer with incontinence for years before symptoms resolve. The financial cost to patients and society reaches into the billions of dollars per year. Data from the SISTEr trial (discussed in more detail below) found that women spent on average $750 per year in out-of-pocket expenses to manage their stress

incontinence. Costs increased significantly with the frequency of incontinent episodes.

PATHOPHYSIOLOGY / EPIDEMIOLOGY OF STRESS INCONTINENCE

In continent women with normal bladder and urethral function, the intrinsic pressure in the urethra exceeds the bladder pressure at all times other than during voiding. Any increase in intra-abdominal pressure from a cough or sneeze is transmitted equally to the bladder and proximal urethra due to the stable retropubic position of the proximal and mid urethra. In continent women, this stabilization of the urethra is postulated to occur via three interrelated mechanisms. The first mechanism is reflex, or voluntary, contraction of the pelvic floor musculature. In women with intact support and/or neuromuscular reflexes, increases in intra-abdominal pressure trigger this reflex contraction of the levator muscles, which elevates the proximal urethra and urethrovesical junction (UVJ) and tightens intact connective tissue supports to maintain urethral closure and prevent leakage.

The second mechanism involves intact connective tissue support to the urethra and UVJ. The pubocervicovesical or anterior endopelvic connective tissue in the area of the UVJ are attached to the posterior pubic symphysis, the arcus tendineus fascia pelvis, and the perineal membrane. The pubourethral ligaments also help suspend the mid-portion of the urethra. These connective-tissue components form the passive supports to the urethra and UVJ. During times of increased intra-abdominal pressure, if these supports are intact, they augment the

supportive effect of muscular contraction and closure of the pelvic floor.

The third mechanism is the two striated muscles, the urethrovaginal sphincter and the compressor urethrae, found at the distal aspect of the striated urethral sphincter. These muscles may aid in compressing the urethra closed during stress maneuvers. These muscles lie along the lateral and anterior aspects of the urethra. DeLancey has suggested that the urethrovaginal sphincter and the compressor urethrae may provide compression and increased pressure in the distal urethra during times of physical exertion. Continence at rest is also maintained by appropriate functioning of the intrinsic urethral sphincter mechanism, which is composed of the submucosal vascular plexus and the urethral smooth and striated muscle.

Multiple anatomic and physiologic theories have been advanced to explain the pathophysiology of stress urinary incontinence. Stress incontinence is thought to result from either failure of the urethral support mechanism leading to urethral hypermobility, or impairment of the intrinsic urethral sphincter in women with intrinsic sphincter deficiency, or both.

Urethral hypermobility is related to impaired neuromuscular functioning of the pelvic floor and compromise of the connective tissue supports of the proximal urethra and UVJ. When the urethra is hypermobile, the reflex contraction of the pelvic floor musculature that normally occurs with increases in intra-abdominal pressure may be compromised as the urethra descends and rotates posteriorly. Intraurethral pressure falls below bladder pressure, resulting in urine loss. Damage

to the nerves, muscle, and connective tissue of the pelvic floor is important in the genesis of stress incontinence with injury during vaginal childbirth probably being the most important mechanism. Aging, hypoestrogenism, history of smoking, chronic connective tissue strain due to primary loss of muscular support, activities, or medical conditions such as obesity, chronic constipation, or chronic cough that result in long-term repetitive increases in intra-abdominal pressure, as well other factors can contribute to urethral hypermobility.

Intrinsic sphincter deficiency (ISD) is a condition in which the urethral sphincter cannot coapt (close) sufficiently to generate enough urethral closure pressure to retain urine in the bladder during times of increased intra-abdominal pressure. In severe cases of ISD, women may experience urinary incontinence with activities that entail minimal increases in pressure on the bladder such as simply standing up from a seated position or bending over. Experts believe that intrinsic sphincter deficiency is due to devascularization and/or denervation of the urethral sphincteric mechanism. Urethral sphincter function diminishes with aging and may become further impaired after vaginal childbirth, pelvic surgery, pelvic radiation, or neurologic injury. The urethral sphincter is also an estrogen dependent tissue and lack of estrogen following menopause leads to atrophy and replacement of the submucosal tissues including the vascular plexus with fibrous tissue. While estrogen replacement has been found to increase blood flow to the urethral vascular plexus and is associated with improvement of collagen fibers in the supportive tissue, studies reveal inconsistent improvement of stress incontinence symptoms following estrogen replacement.

NONSURGICAL MANAGEMENT OF STRESS INCONTINENCE

The nonsurgical treatments of stress incontinence are designed to reverse the functional causes of urinary incontinence and correct the underlying pathophysiology of SUI, by correcting either urethral hypermobility and/or improvement of urethral coaptation. Behavioral approaches can include improvement of fluid and voiding habits, smoking cessation, control of allergies and comorbid pulmonary conditions, adjustments of medications, weight loss, and changes in exercise routines to reduce the extent of increases in intra-abdominal pressure on the bladder and urethra.

Pelvic floor muscle exercises (PFE) are one of the most commonly recommended treatments for stress incontinence. Patients are told to practice contracting and relaxing the levator muscles to improve resting tone and the ability of the patient to contract her pelvic floor muscles to voluntarily. The goal of PFE are to improve resting pelvic muscle resting tone and to augment tone by voluntarily contracting the muscles during stressful activities. PFE are also thought to reduce overactive bladder contractions by improving urethral resistance and preventing urine from entering the proximal urethra. Although PFE have been advocated for decades, no standard protocol of exercises has been found to be superior, and not all women see clinically meaningful improvement from PFE. If a woman is able to learn "the knack" of rapid recruitment of the muscles during a cough or sneeze, she may be able to reduce or prevent incontinence, if her SUI is mild and occurs only during brief increases in intra-abdominal pressure. Women suffering from incontinence

during more prolonged activities such as brisk walking, running, exercise or jumping are unable to sustain the muscle contraction and are less likely to benefit from PME. Some patients may have damage to their pelvic floor innervation or muscles and are unable to contract their pelvic muscles or recruit the correct muscles despite coaching. A review of over 20 studies evaluating the efficacy of PFE has found occasional improvement of stress incontinence, however, long-term results are disappointing. At 5 years, 25% found no change in their symptoms and up to 50% were no longer doing the exercises. At 15 years, only 25% were continuing the exercises and 50% had undergone surgical treatment of their stress incontinence. Adding bladder training and/or biofeedback to a PFE routine does not appear to improve the efficacy of PFE alone. The efficacy of electrical stimulation for stress incontinence has been inconsistent although a RCT of active stimulation versus sham stimulation did find some improvement in the treatment group.

There are no FDA approved **medications** for the treatment of stress urinary incontinence although several drugs have been used off-label with the goal of improving urethral tone. Alpha-adrenergic agents usually cannot be given at sufficient doses without significant side effects. Imipramine, a tri-cyclic antidepressant with alpha-agonist and anti-cholinergic effects, has been reported anecdotally to reduce both stress and urge incontinence symptoms. Duloxetine, a selective norepinephrine and serotonin inhibitor, has been used outside of the United States for stress incontinence with up to 50% of women noting a $\geq$ 50% reduction in diary-confirmed incontinent episodes.

Pelvic or urethral support devices such as pessaries or incontinence rings are latex, silicone, or rubber devices placed in the vagina to support and stabilize the urethra and can be left in place for up to one week. Some patients may benefit from the occasional use of a vaginal tampon or the recently marketed Poise Impress product to support the urethra; however, these products need to be inserted and removed daily. Support devices may be useful in women with mild SUI or who want to delay surgical treatment or who desire further childbearing. Because pessaries or rings require optimal fitting and patient care at home, they are not an option for all women. Successful fitting has been reported between 71–89% of subjects, with more difficulty fitting women s/p hysterectomy, TVL <6cm, GH >4cm or patients with concomitant posterior wall relaxation. After 6 months, 55–89% of women are still using the device. A 2011 Cochrane review concluded there was little evidence to judge if a pelvic support device was any better than no treatment. When behavioral therapy was compared to pessary in the ATLAS trial, at 12 months no difference was seen either between treatment groups or in the group that received combination therapy.

Urethral Bulking Agents are designed to improve the urethral coaptation by transurethral or peri-urethral injection of material under the epithelium of the proximal urethra. As the procedure can be performed in an office or surgi-center under local anesthesia (with or without intravenous sedation), it can be an alternative for women with significant medical co-morbidities or those who decline more invasive surgical intervention. Outcome data has not indicated an optimal injection route or material, although women without urethral hypermobility may be

better candidates for a bulking agent. The first FDA approved material was glutaraldehyde cross-linked bovine collagen (Contigen), which has been discontinued by the manufacturer. Current bulking agents are non-biodegradable, synthetic products including carbon-coated zirconium beads, silicone, calcium hydroxylapatite and ethylene vinyl alcohol. Migration of particles and granuloma formation with carbon coated zirconium beads have been reported in patients. Silicone bulking material has been thought to be involved with the development of auto-immune disorders in a rare number of patients. Other complications include persistent or recurrent stress incontinence, voiding difficulty necessitating catheter drainage, urinary tract infections, suburethral sterile and non-sterile fluid collections causing urethral obstruction and urethra-vaginal fistulas. Additionally, women who experience suboptimal and/or only short-term improvement with urethral injections will often elect to undergo conventional surgery such as a mid-urethral sling.

SURGICAL TREATMENT OPTIONS FOR STRESS INCONTINENCE

Over the past century more than 200 surgical procedures have been described for the treatment of stress urinary incontinence, indicating the challenge of achieving optimal long-term results for women with this condition. Early in the 20th century surgical procedures for stress incontinence were vaginal operations designed to correct prolapse of the urethra and the anterior vaginal wall. **Anterior colporrhaphy and the Kelley plication** utilize mattress sutures to plicate the anterior endopelvic fascia and provide support for the urethra and bladder. Despite

longstanding anecdotal evidence regarding the success of this procedure, the results of better-designed, long-term studies have been disappointing. A meta-analysis in the early 1990s reported 1-year subjective and objective cure rates of 81% and 71%, respectively; while Bergman found 1-year cure rates of 65% and 5-year rates of only 37%. Post-operative complications were infrequent with de novo symptoms of bladder overactivity in 6% and major complications in less than 5% of women. Despite its relative low morbidity of anterior colporrhaphy, its substantially higher failure rate, especially when compared to retropubic operations, has led to the abandonment of anterior colporrhaphy as a treatment option for stress urinary incontinence.

RETROPUBIC COLPOSUSPENSIONS

Marshall, Marchetti, and Krantz first described an abdominal retropubic operation for stress incontinence in 1949. Initially, absorbable sutures were placed bilaterally partially within the urethra and bladder neck, but later moved to the anterior vaginal wall just lateral to the urethra. Once placed, the sutures were secured to the periosteum of the pubic symphysis. The surgical outcome of the MMK was superior to anterior colporrhaphy with a review of 56 articles involving over 2700 patients reporting a subjective success rate of 92% for primary procedures and 84% for repeat operations. At 5 years, subjective continence was achieved in 86% and 75% after 15 years. Post-operative complications occurred in 21% including urethrovaginal fistula, osteitis pubis, long-term voiding disorders and de novo detrusor instability.

Abdominal or vaginal paravaginal repairs are designed to restore vaginal and urethral support when the lateral vaginal attachments to arcus tendineus have been compromised. Reattachment sutures are placed anteriorly from where the arcus tendineus inserts into the pubic symphysis and proceeding posteriorly and laterally to its attachment at the ischial spine. Although some surgeons have relied on this approach to treat stress incontinence, it is less effective than other retropubic colposuspension operations, and usually reserved for correction of anterior compartment prolapse due to lateral defects. In one RCT, the vaginal paravaginal repair was associated with a higher incidence of pudendal neuropathy compared to the abdominal approach.

The initial **Burch colposuspension** was similar to the paravaginal repair where sutures were placed in the vagina inferior to the edge of the bladder and lateral to the urethra and anchored to the anterior portion of the arcus tendineus. However, given the variable integrity of the anchoring point, results were suboptimal. Burch subsequently chose the stronger iliopectinal ligament as his preferred site of attachment. Tanagho modified the Burch procedure by placing sutures in the anterior vaginal wall at the urethrovesical junction and more distally along the urethra and suspending this tissue to the iliopectinal line. The improved success rates of the Burch procedure compared to anterior colporrhaphy and other retropubic operations made it the "gold standard" for many decades. However, given the anterior displacement of the vaginal axis related to the Burch procedure, this operation has been associated with a 15–20% rate of subsequent apical or posterior support defects (enterocele and rectocele formation). To reduce the risk

of future enterocele formation and/or apical prolapse following a Burch procedure, some surgeons perform a concomitant cul-de-sac obliteration at the time of Burch procedure. This increases the risk of the operation by requiring entry into the peritoneal cavity and increasing OR time.

The 2012 Cochrane review of open retropubic colposuspensions included 53 studies and 5,244 women reporting an overall success rate of 68.9–88.0%, with a failure rate of 15–20% within the first 5 years following surgery. The open retropubic colposuspension procedure was also more efficacious than anterior colporrhaphy and needle suspension procedures in a meta-analysis of 8 RCTs and 10 RCTs, respectively. In up to 5-year follow-up, the Burch procedure was associated with less post-operative incontinence than the MMK procedure. However, longer-term follow-up has found significant urinary incontinence in 56% of women at 14 years after a Burch procedure while only 19% of patients remained dry. (**Kjolhede** 2005)

PUBOVAGINAL SLING PROCEDURES

Pubovaginal sling procedures have been described for over 100 years. Because of the increased risks of complications associated with the operation, slings were initially reserved for women with severe recurrent stress incontinence or Type III incontinence (ISD). The strip of sling material under the urethra is believed to provide better support to the urethra and some degree of external compression to compensate for urethral hypermobility and a poor intrinsic sphincter than can be accomplished by peri-urethral suture placement in the retropubic procedures. A

traditional pubovaginal sling requires an extensive dissection of the periurethral tissues to allow sharp or blunt dissection through the endopelvic fascia into the retropubic space. A 4-5 cm suprapubic incision is also needed to gain access to the attachment site of the sling, either at the rectus fascia or posterior pubic symphysis. An instrument is then passed from the abdominal incision to the vaginal field lateral to the urethra to retrieve each end of the sling in a "top down" approach. Traditional slings are placed under the bladder neck and proximal urethra, and are usually at least 2 cm in width to distribute pressure over the urethra and to minimize banding or transection of the urethra. The more extensive dissection of the peri-urethral tissues is thought to be associated with the increased risk of urinary tract injury and de novo urgency and urge incontinence associated with the traditional slings. A significant challenge for surgeons performing pubovaginal slings has been determining the correct amount of sling tension, especially in women with intrinsic sphincter deficiency and/or reduced detrusor contractility. The lack of a reliable tensioning technique accounts for the increased post-operative voiding dysfunction following traditional pubovaginal sling surgeries. Another concern with sling procedures is the potential risk of infection associated with implantation of a sling through the non-sterile vaginal field. Over 50 years ago, Millin and Read performed pubovaginal sling procedures solely through an abdominal incision, bringing a single strip of rectus fascia inferiorly behind the pubic symphysis and tunneling between the urethra and the vaginal wall without a vaginal incision. This approach has been advocated by one plaintiff expert (Dr. Rosenzweig) as the optimal technique for insertion of a sling without publishing

data on his results. Millin and Read ultimately abandoned this approach after encountering higher rates of urethral injury.

The choice of sling materials has changed dramatically over the past 100 years, from the use of muscle flaps to biologic materials to absorbable or permanent synthetic mesh. Each material is associated with a risk-benefit profile. Autologous grafts have the potential advantage of biocompatibility, which limits the risk of autolysis or untoward tissue reactions at the graft site. Autologous grafts used in incontinence surgery are typically harvested from the patient's rectus fascia or fascia lata (outer thigh). However, these approaches increase operative time, operative morbidity and post-operative recuperation. Harvesting an adequate strip of rectus fascia typically requires a long abdominal incision (usually at least 15 cm) increasing the risk of infection, pain or subsequent hernia formation. A fascia lata sling necessitates a second operative site that is susceptible to infection and pain, and has been reported to compromise knee stability in rare patients.

Allografts harvested from cadavers provide a graft that has been processed to minimize the likelihood of subsequent tissue degradation and the risk of transmission of infectious material such as prion or viral particles. However, allografts have also been associated with stretching and/or degradation of the biologic material and a higher risk of recurrent stress incontinence. Additional concerns are the higher cost, availability of the product, variable quality of the tissue samples, and the detection of host DNA despite specimen processing.

The primary xenograft used in pelvic reconstructive surgery has been porcine dermis, which is designed to be a permanent biologic material. Porcine dermis is extremely dense, more difficult to handle and requires extra time intra-operatively to fashion a feasible sling. Erosion, extrusion, and degradation of the material have also been encountered with porcine dermis. Potential issues with biologic grafts also include the reluctance of some patients to have their own tissue harvested from another part of their body for this procedure or the reluctance to have cadaver tissue or porcine tissue incorporated into their body.

Because of the above challenges with biologic sling materials, many investigators have explored the use of synthetic materials. The biomechanical properties of a synthetic mesh in vivo depend on: 1) the type of fiber, 2) the size of the fiber, 3) the type of weave, 4) the pore size of the material, 5) the mesh density and 6) surface area of the mesh. Fibers may be monofilament (e.g. polypropylene) or multifilament (e.g. polyethylene) and composed of thinner or thicker filaments that are permanent or absorbable. Meshes are composed of either single or multiple types of individual fibers that are typically woven or knitted together into sheets of mesh that are then fashioned into a strip of material intra-operatively by the surgeon. Woven fiber meshes demonstrate a higher likelihood of fraying at cut edges compared to knitted materials. When cutting or shaping a mesh is required, as in pelvic reconstructive surgery, a knitted mesh is preferable. Important factors that determine the tissue biocompatibility of non-absorbable meshes are the type of fibers, the size of the fiber, the mesh density, and porosity of the mesh. Multifilament fiber meshes are more susceptible to bacterial adherence, infection

and symptomatic chronic inflammatory reactions leading to scarring and are not recommended for use in vaginal surgery. Microporous materials (such as expanded polytetrafluoroethylene) with a pore size <10 μm do not allow for the infiltration of macrophages, fibroblasts, blood vessels or collagen. Lack of infiltration prevents a microporous mesh from being incorporated into tissue, which was initially thought to be beneficial by reducing the risk of scarring. However, microporous slings have been associated with up to a 20% risk of re-operation for removal due to host reactions including erosion, extrusion and/or chronic sinus tract formation. Macroporous monofilament meshes (>75 μm) allow for infiltration of the macrophages, fibroblast and collagen improving tissue incorporation and reducing the risk of bacterial adherence to the mesh.

Reports on the efficacy of pubovaginal slings vary widely in the literature depending on the type of sling material and the definitions of success or cure, ranging from 60–93%. Autologous slings tend to have higher cure rates than allograft slings. The 20–40% failure rate reported with cadaveric fascia lata is thought to be due to autolysis and resorption of the material. The most commonly used xenograft is porcine cross-linked dermis with 1-year cure rates as low as 22% in a RCT, while another trial reported 5-year cure rates of 89%. Success rates using synthetic slings materials have approached 80–90% in some series.

A comprehensive prospective randomized trial of the surgical treatment of stress incontinence, the SISTEr trial, compared the efficacy and complications of the Burch colposuspension and autologous fascial sling in 655 women enrolled in the

trial. Follow-up at 2 years, 5 years, and 7 years have been published with substantially lower cure rates for both procedures than has previously been reported. Cure at 2 years was defined objectively as no leakage on a 3-day diary, a negative cough stress test, no self-reported symptoms of incontinence and no re-treatment for urinary incontinence. The results of the 326 women who underwent the fascial sling were better than the 339 women in the Burch group with a 2-year success of 66% and 49% respectively. Results at 5 and 7 years were based on patient questionnaire, 3-day diary, and no re-treatment for stress incontinence. Subjective success in the Burch group was 24.1% and 13% in the women followed for 5 years and 7 years, whereas the fascial sling group 30.8% and 27% subjective cure at 5 years and 7 years, respectively.

The SISTEr trial also provided insight on the adverse events associated with the most commonly performed surgeries prior to the introduction of the mid-urethral slings (MUS). Serious adverse events were defined as any complication requiring another surgical procedure. Since many women undergoing surgery for stress incontinence have other procedures performed concomitantly, the authors examined the complications in women with concomitant surgeries and those who only had a procedure for stress incontinence. Overall 47% of the Burch group and 63% of the autologous fascial sling group experienced some adverse event. Serious adverse events (SAE) such as wound infections, abscess, hematoma, gastrointestinal complications, subsequent ventral hernia, or enterocele were noted in 10% of the Burch group. Similar serious adverse events as well as problems with vaginal tissue healing or graft reactions were found in the autologous fascial sling group (SAE

13%). In patients only having surgery for stress incontinence, SAE still occurred in 7.3% of women, with 48% experiencing some adverse event including a 9–10% risk of recurrent urinary tract infections or voiding dysfunction at 24 months.

In a 2013 review of surgical management of stress incontinence, Cox et al concluded that autologous pubovaginal slings are indicated in women who have failed other incontinence procedures, who require a concomitant urethral reconstructive procedure for urethral diverticulum or fistula, or who have experienced mesh complications such as urethral erosion.

DEVELOPMENT OF TVT AND TOT MINIMALLY INVASIVE SLINGS

The rationale for a new, minimally invasive procedure for the treatment of stress incontinence was predicated on the following factors:

- The recognition that anterior colporrhaphy is a minimally invasive vaginal procedure for the treatment of stress incontinence but is associated with an unacceptably high rate of persistent and/or recurrent incontinence.
- Although abdominal retropubic procedures were the "gold standard" surgical approaches for stress incontinence, the operations required a more invasive abdominal incision with its inherent risks, longer operating time, longer hospital stay and slower post-operative recovery, especially given that in the mid-1990s relatively few

surgeons had developed the operative skills required for the more complex laparoscopic retropubic procedures.

- The understanding that women with recurrent incontinence or ISD experienced better resolution of their stress incontinence following a pubovaginal sling compared to an anterior colporrhaphy or retropubic operation; but with a traditional sling, these patients underwent a more invasive surgery and risked higher rates of voiding dysfunction and/or overactive bladder symptoms.
- The optimal biologic or synthetic sling material had yet to be developed.

In an attempt to create a more patient-friendly and user-friendly operation for stress incontinence, in 1995 Ulmsten began employing previously recognized sling materials—polytetrafluoroethylene (Gore-Tex) and polyethylene terephthalate based polyester (Mersilene)—in a novel, minimally invasive mid-urethral sling procedure. After noting an 8–10% rejection/erosion rate for these initial materials, Ulmsten turned in 1996 to polypropylene mesh in developing the prototype for the Ethicon TVT procedure. The uniqueness of the TVT procedure (and its subsequent modifications) remain:

- The procedure could be performed under local anesthesia as an outpatient reducing anesthetic risks, operating time, hospitalization, costs and post-operative recovery time. This ability was due to the smaller vaginal and abdominal incisions, less dissection near the

proximal urethra and bladder neck, and the specially designed trocars for passage of the sling.

- The sling is positioned under the mid-urethra, rather than under the proximal urethra as in previously described pubo-vaginal sling operations. Ulmsten and his colleagues proposed that urethral continence is due to the complex coordination of three structures—the pubourethral ligament, the suburethral vaginal hammock and the pubococcygeus muscle. Coining the term the "integral theory" of stress incontinence, they postulated that failure of the pubourethral ligament to adequately support the urethra resulted in stress incontinence. Positioning a narrower, 1.0 cm wide tape at the mid-urethra, the location of the maximum urethral pressure, compensated for the weakened pubourethral ligament and created the equivalent of a "knee" for the urethra. Ulmsten warned that more proximal placement near the bladder neck would increase the risk of voiding difficulties.
- Placement of the tape in a tension-free position without anchoring the distal ends of the material to the rectus fascia or pubic symphysis to avoid excess tension on the urethra and the concomitant voiding problems. The "strong adhesive effect" due to "the properties of the sling material" prevented sliding of the sling but required employing a plastic sheath to allow adjustment of the sling during positioning and to "prevent the sling from becoming contaminated at implantation".

In October 1997, Ethicon submitted a 510(K) application to the FDA who granted clearance of the retropubic TVT minimally invasive mid-urethral sling in January 1998. Justification for the polypropylene sling material was based on:

- The long-standing and widespread use of polypropylene suture as a safe and effective material employed in nearly every surgical discipline when permanent monofilament suture is required.
- Over half a century of experience with polypropylene mesh as a surgically implantable prosthetic for abdominal hernia repair and the recognition that polypropylene is "one of the most inert materials implanted in humans".
- Cytotoxicity Testing showing non-cytotoxicity of polypropylene mesh by ISO agarose diffusion, extraction, and overlay testing. While cytotoxicity was evident by ISO elution testing, in previous elution testing of the potentially more reactive non-sterile, raw polypropylene, non-cytotoxicity was demonstrated.
- Biocompatibility was assessed in approximately 500 patients who underwent TVTs prior to submission concluding that "the potential cytotoxicity of the polypropylene mesh observed in vitro (in ISO elution testing) does not translate into any clinical significance".

As a surgeon and medical doctor who has implanted the Ethicon TVT, I am in agreement. As discussed further below, the voluminous clinical data since has confirmed the safety and efficacy of mid-urethral sling procedures.

The transobturator approach (TVT-O) for a mid-urethral sling was later introduced based on the "hammock theory" of urethral support and function. By avoiding the retropubic space and placing the tape via an inside-out passage through the obturator membrane and obturator internus muscle, the TVT-O was designed to reduce the risk of bladder perforation and vascular and bowel injuries—rare complications of the retropubic approach. The TOMUS trial compared the results at 12 months of 597 women with stress incontinence who were randomized to a retropubic TVT or a TVT-O. Subjective and objective cure rates were not statistically different between the two treatment groups, although the rates are lower than other reported trials. Voiding dysfunction was infrequent (3.4% and 1.3%) and not statistically significant. Other meta-analyses have confirmed equivalent success rates for the two procedures with some variations in procedure specific adverse events such as bladder perforation or groin/leg pain. Most surgeons prefer one approach over the other based on their individual experiences.

LONG-TERM DATA

Since their inception, there has been a plethora of data demonstrating the long-term safety and efficacy of minimally invasive mid-urethral sling procedures such as the Ethicon retropubic TVT and TVT-O procedures. Minimally invasive mid-urethral sling procedures (MUS) have now become the "gold standard" for surgical treatment of stress incontinence. In 2004, the 7-year follow-up data from the original Scandinavian multi-centered TVT trial reported objective and subjective

cure rates of 81.3% for the 80 women available for follow-up. Other than asymptomatic pelvic prolapse (7.8%), de novo urge symptoms (6.3%), and recurrent urinary tract infections (7.5%), no long-term adverse effects were detected. The eleven-year follow-up results from three Nordic sites reported 77% subjective cure rate with 20% improved and no episodes of tape erosion. The seventeen-year follow-up results reported a 91% objective cure rate, 87% were subjectively cured or significantly improved, and there was one case of a minimal, asymptomatic mesh exposure in a patient who was still satisfied with the results of her surgery. The authors noted that this patient had atrophic vaginal mucosa, which increases the risk of tape exposure. Additionally, no clinically relevant shrinkage of the mesh was observed over time as there was no increase in post-void residual volumes. Numerous other studies that assessed the retropubic TVT for ten years or more demonstrate similar efficacy and safety as Nilsson's series. These include the eleven-year follow-up by **Olsson**, the ten-year follow-up by **Groutz**, the ten-year follow-up by **Aigmueller**, the ten-and-a-half-year follow-up by **Heinonen**, the ten-year follow-up by **Serati**, and the ten-year, nine-month follow-up by **Svenningsen**.

Since 2010, multiple 5-year (medium term) and over 10-year (long-term) reports have been published regarding the safety and efficacy of MUS procedures including the Ethicon TVT and TVT-O. These reports include case series, RCTs, and registry data utilizing more specific outcomes measures than were employed in the several decades preceding the introduction of MUS when the long-term results of

alternative procedures such as needle suspension operations, open Burch retropubic procedures, and traditional suburethral slings were published.

In 2014, **Laurikainen** reported the 5-year outcome of a multi-centered RCT comparing retropubic and transobturator MUS in 7 Finnish hospitals using objective treatment success criteria of negative stress test, negative 24-hour pad test and no retreatment for SUI. Laurikainen had an outstanding follow-up rate of 95% at 5 years even with women lost to follow-up categorized as failures. The 5-year objective cure rate was similar in both groups with 84.7% in the retropubic group and 86.2% in the transobturator group. Complication rates were low, with no difference between groups. No late-onset adverse effects of the tape material were seen and the authors noted "no woman had any sign of tissue reaction, erosion or tape protrusion at their 5-year follow-up". **Heinonen** (2012) published 10-year data on 138 patients following MUS procedures with 72% follow-up. He found 90% objective cure rate and only 3 patients (2.3%) with late adverse effects: 1 (0.8%) mesh erosion into bladder and 2 (1.6%) with retention and pain that resolved with cutting of the tape.

In 2010, **Olsson** reported on the greater than 10-year objective outcome of 104 women (84% follow-up) who comprised Ulmsten's original, open, prospective 6-center retropubic MUS study. At more than 10 years follow-up, the objective success rate was 84% and no late adverse effects of the operation despite intra-operative complications including 2.7% bladder perforation and 1.4% urethral injury in the original report.

Serati and colleagues published 10-year objective and subjective outcomes for a retropubic MUS procedure in 55 women (92% follow-up) enrolled in a multicenter trial. "The 10-year subjective, objective, and urodynamic cure rates were 89.7%, 93.1%, and 91.4%, respectively. These rates were stable across the whole study period (p>0.99). De-novo overactive bladder was reported by 30.1% and 18.9% of patients at 3-months and 10-year follow-up, respectively (p for trend = 0.19). No patient required sling release over the 10-year follow-up period. In 2015 Serati reported their 13-year follow-up; 47 out of 55 (85.5%) patients were re-evaluated with "no significant deterioration of objective cure rates was observed over time (P = 0.29)".

In 2013 **Svenningsen** reported the 10-year data from the initial 603 women included in the Norwegian retropubic MUS registry. Overall 80% of women were successfully contacted and 54.2% (327 women) were clinically evaluated. Objective cure rate, defined as a negative stress test, was 89.9% and subjective cure rate, defined via a validated urinary incontinence questionnaire, was 76.1%. Only 2.3% of the women had undergone repeat SUI surgery. De novo urgency incontinence increased significantly from 4.1% at 6–12 months after surgery to 14.9% at the 10-year follow-up. A secondary risk analysis by Svenningsen was published in 2014, which found that patient age ≥56 years old at the time of surgery, a history of severe preoperative urgency incontinence component or surgical complications seem to represent independent risk factors for long-term (10-year) failure.

RANDOMIZED CLINICAL TRIALS, SYSTEMATIC REVIEWS, AND META-ANALYSES COMPARING MID-URETHRAL SLING PROCEDURES TO OTHER PROCEDURES FOR STRESS INCONTINENCE

In 2009 the Cochrane Database Review by **Ogah** of 62 trials and over 7100 women showed MUS procedures to be as effective as a traditional suburethral slings (RR 1.03, 95% CI 0.94–1.13) with shorter operating time and less post-operative voiding dysfunction and de novo urgency symptoms. Ogah also found that at 5-year follow-up, MUS were found to be as effective as open retropubic procedures (RR 0.91, 95% CI 0.74–1.12) with shorter operative times and hospital stays, less peri-operative morbidity except for a higher rate of bladder perforations, and less post-operative voiding dysfunction. Monofilament mesh tapes were associated with only a 1.3% rate of mesh erosion in this large number of women. Six trials have compared MUS procedures to laparoscopic Burch procedures with no difference in subjective cure rates at 12 months. Although there was no difference in peri-operative complications or post-operative voiding dysfunction, the MUS patients had shorter operative times and hospital stay, and fewer de novo post-operative urgency and urge incontinence symptoms compared to laparoscopic retropubic urethropexies. Multiple other authors such as **Novara** and professional organizations such as American Urological Association (AUA) who have conducted meta-analyses of over 10,000 women following MUS procedures have reported similar findings.

In 2014, **Schimpf** published the Society for Gynecologic Surgeons (SGS) Systematic Review Group's meta-analysis comparing surgical procedures for stress incontinence. Their exhaustive review of 881 papers from 1990 through April 2013 yielded 49 randomized clinical trials with a minimum of 12 months of follow-up for comparative analysis of success rates and another 39 reports that were included in their summary of adverse events. They concluded that the "retropubic MUS, specifically the TVT, is the best-studied procedure" and "overall, the evidence supporting use of MUS ... is of high quality". Based on my long-standing review of the medical literature I agree with this conclusion.

In July 2015, **Ford** published the most recent Cochrane review evaluating the clinical effects of MUS operations for the treatment of SUI, urodynamic stress incontinence (USI), or mixed urinary incontinence (MUI) reported in randomized or quasi-randomized controlled trials amongst women with SUI, USI or MUI, in which both trial arms involved a MUS operation. The review included 81 trials that evaluated 12,113 women. Of the 81 trials, 55 trials with 8,652 women compared the use of the transobturator route and retropubic route. The authors reported that there is moderate quality evidence that in the short term (up to one year) the rate of subjective cure of transobturator and retropubic MUS are similar (RR 0.98, 95% CI 0.96–1.00; 36 trials, 5514 women) ranging from 62% to 98% in the transobturator group, and from 71% to 97% in the retropubic group. Short-term objective cure was also similar in the transobturator and retropubic groups (RR 0.98, 95% CI 0.96–1.00; 40 trials, 6145 women). The Cochrane reviewers stated that "fewer trials reported medium-term (one to five years) and longer-term (over five years) data,

but subjective cure was similar between the groups (RR 0.97, 95% CI 0.87–1.09; 5 trials, 683 women; low-quality evidence; and RR 0.95, 95% CI 0.80–1.12; 4 trials, 714 women; moderate-quality evidence, respectively). In the long term, subjective cure rates ranged from 43% to 92% in the transobturator group, and from 51% to 88% in the retropubic group." They also concluded that a retropubic bottom-to-top route—as utilized with the Ethicon retropubic device—was more effective than top-to-bottom route for subjective cure (RR 1.10, 95% CI 1.01–1.19; 3 trials, 477 women; moderate-quality evidence). It incurred significantly less voiding dysfunction, and led to fewer bladder perforations and vaginal tape erosions.

According to Ford and colleagues, the overall rate of adverse events for MUS procedures remained low. There were only limited data to inform the need for repeat incontinence surgery in the long term, but it was more likely in the transobturator group than in the retropubic group (RR 8.79, 95% CI 3.36–23.00; 4 trials, 695 women; low-quality evidence). The rate of bladder perforation was 2.5% (transobturator 0.6% versus retropubic 4.5%; RR 0.13, 95% CI 0.08–0.20). Postoperative voiding dysfunction was less frequent following transobturator procedures (RR 0.53, 95% CI 0.43–0.65; 37 trials, 6200 women; moderate-quality evidence).

Overall rates of groin pain were higher in the transobturator group compared to the retropubic group (6.4% versus 1.3%; RR 4.12, 95% CI 2.71–6.27), whereas suprapubic pain was lower in the transobturator group (0.8% versus 2.9%; RR 0.29, 95% CI 0.11 to 0.78). Most women had resolution of pain within 6 months

following surgery; mean time for resolution was 8 weeks with a range of 2–52 weeks. Sexual function was evaluated in 10 trials with the reviewers stating that the "reported occurrence of problems with sexual intercourse including pain was low."

The overall rate of vaginal tape erosion/exposure/extrusion was low in both groups: 24/1000 (2.4%) with transobturator approach compared with 21/1000 (2.1%) for retropubic procedures like the Ethicon TVT procedure (RR 1.13, 95% CI 0.78–1.65; 31 trials, 4743 women; moderate-quality evidence). The authors' conclusions are consistent with other earlier Cochrane Reviews of MUS in that they state that these "operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI."

COMPLICATIONS OF MUS VERSUS OTHER SURGERIES FOR STRESS INCONTINENCE

Every surgical procedure for stress incontinence is associated with procedure dependent and independent risks of complications. Analysis and comparison of complication rates in early and current literature is hampered by the quality of the study and the surgeon's willingness to report operative complications and/or disasters. Many of the earlier studies published on the outcomes of Burch colposuspension and pubovaginal sling procedures did not specifically describe all

complications, failed to even consider quality-of-life and sexual-function parameters, and often had rather short length of follow-up. The introduction of MUS procedures, such as the Ethicon retropubic TVT and TVT-O, corresponded with realization by clinical investigators, national specialty societies, and NIH- and industry-sponsored researchers that surgical trials must compile and publish more comprehensive and objectively defined complication rates. Thus, the more recent literature describing the complications of SUI procedures such as the MUS is more detailed than older studies published regarding the experience with traditional slings or abdominal retropubic operations. This improvement in the quality of newer studies can appear to skew comparative data on complication rates of the different procedures.

The most reliable comparative data comes from more recent RCTs with adequate patient enrollment and follow-up (SISTEr, TOMUS) and meta-analyses of previously published smaller RCTs. The SISTEr trial reported that 48% of 275 women undergoing just a Burch or sling for stress incontinence had at least one adverse event, and 7.3% experienced a SAE requiring return to the OR for genitourinary complications, bleeding or wound problems. One of the most comprehensive comparisons of operative complications from different procedures for stress incontinence was compiled by the SGS Systematic Review Group and published in 2014. According to their analysis, MUS had a lower rate of peri-operative adverse events compared to either a Burch or pubovaginal sling for blood loss, operating time, and hospital stay; and a lower rate of bowel injury, wound infections, hematoma and post-operative pain than a Burch procedure. While MUS

procedures did not differ compared to traditional pubovaginal slings with respect to return to the OR for material erosion or urinary retention, MUS may be associated with a higher rate of return to the OR compared to a Burch colposuspension for problems due to urinary retention, erosion, OAB symptoms, and groin pain (TVT-O). When comparing retropubic MUS and obturator MUS, each was associated with higher rates of procedure-specific adverse events. Retropubic MUS resulted in lower rates of overall erosions and need to return to the OR for erosion, groin or leg pain, and vaginal perforation; whereas obturator approaches had fewer bladder or urethral injuries, less overactive bladder symptoms and post-operative pain, and fewer urinary tract infections.

In 2015, **Tommaselli** and colleagues published a meta-analysis of the long-term outcomes of retropubic MUS procedures after 60 months, and the medium-term outcomes of transobturator MUS procedures after 36 months when either was compared to another synthetic sling procedure. The review evaluated 49 studies including 11 RCTs and 38 non-randomized trials, and concluded that MUS performed either via retropubic or transobturator route "have similar objective cure rates" although a transobturator approach had slightly lower subjective cure rates. Complication rates were similar to other published series and are summarized in the following table.

Table 1. Summary of post-operative complications Tommaselli et al.

Complication	Retropubic MUS	Transobturator MUS	p-values
Bladder/Urethral Injury	2.4	0.4	p<0.001
Vaginal Injury	0.4	3.3	p=0.02
Hematoma/Bleeding	3.7	3.9	
Urinary Retention	5.4	4	
De novo Urgency	10	10.2	
Pain	1.8	5.7	p<0.001
Tape Erosion	2.1	2.7	

Tommaselli noted that complications were "seldom severe". Of note is that pain was defined as a complication if patients had any post-operative pain after 7 days following surgery. I believe the authors' definition of pain as a complication is clinically unrealistic in women who are only a week after surgery. Persistent or chronic pain (which the authors defined as "pain persisting beyond the perioperative period or reported at the last follow-up visit") was reported by 13 of the 3,974 patients receiving retropubic slings (0.3%) and only 30 of the 2,432 patients receiving transobturator slings (1.2%) reported persistent or chronic pain.

RISK OF RE-OPERATION FOLLOWING MUS PROCEDURES

In addition to the studies referred to above that address the success rates and complications associated with MUS procedures, other series have looked at the risk of re-operation following MUS operations. The indications for re-operation following a mid-urethral sling include: voiding dysfunction, mesh erosion or extrusion, persistent pain, and persistent or recurrent SUI. Overall, the data indicates re-operation for mesh erosion or extrusion occurs in 1–3% of patients and in 0.6–1.2% for voiding dysfunction. These statistics are consistent with my clinical experience.

Unger and colleagues published a case controlled series in 2015 evaluating the indications and prevalence of re-operation in 3,307 women who had a MUS procedure at the Cleveland Clinic from 2003–2013. Retropubic procedures were performed in 42.7% of patients and 44.9% were transobturator procedures, and 71.2% underwent a concomitant prolapse operation. Overall, 2.7% of the MUS patients underwent sling revision with a median time of 7.8 months (2.3–17.9 months) from the index surgery. Risk of sling revision was not correlated with the type of MUS procedure performed or the type of sling placed. The most common indication for revision was urinary retention (43.8%) followed by voiding dysfunction (42.7%), recurrent urinary tract infections (20.2%), mesh erosion (21.3%), vaginal pain/dyspareunia (7.9%), and groin pain (3.4%). Revisions for urinary retention were performed at a significantly shorter post-operative interval

than other indications. Following revision, 30.7% of patients reported no improvement or worsening of symptoms; all had undergone revision for urinary retention or voiding dysfunction.

In 2015 Welk reported on the risk of sling removal or revision based on the experience of the implanting surgeon. He assessed 59,887 patients in Ontario, Canada from 2002 to 2012 and found an overall complication rate of 2.2% with a 10-year cumulative incidence of mesh revision of 3.3%. Patients of low-volume surgeons (<25th percentile surgical volume per year) had a 37% higher relative risk of mesh revision or removal compared to patients of high-volume surgeons (>75th percentile surgical volume). The finding that more experienced surgeons have higher success rates and fewer post-operative complications with MUS procedures is not surprising. Similarly, a less experienced surgeon may have lower success rates and/or more complications using a particular device, even when the device is properly designed.

Several large population-based studies have addressed the risk of re-operation over time from the index sling surgery. **Nguyen** (2012) reported on 3,747 Kaiser patients who underwent a variety of MUS procedures over a 32-month period. Retropubic procedures were performed in 63% of women and transobturator procedures in 37% of women. Ethicon products were used in 42% of the retropubic and 37% of the transobturator approaches, respectively. Re-operation for voiding dysfunction occurred in 1.3% at a mean of 80 days (range 7–358 days); for vaginal mesh erosion in 0.8% at a mean of 175 days (range 46–388

days); for urethral erosion in 0.08%; and excision for pain in only 1 patient (0.03%). There was no difference in the rate of re-operation based on the device manufacturer. In 2013 **Funk** published data on 188,454 non-Medicare patients from 2001–2010 regarding the cumulative risk of re-operation over a 9-year period from the index surgery. Excluding repeat surgeries for SUI, the overall cumulative risk of re-operation was 3.7%, with 1.3% for urinary retention and 2.5% for mesh erosion. The one-year risk of revision was 2.2%, with the risk continuing to increase yearly until a 4-year of 3.2% after which time it plateaued. The authors concluded "a majority of the sling revisions/removals occurred within the first few years after the index surgery". The risk of mesh erosion was also elevated among women who had a concomitant anterior repair (HR 1.18, 95% CI 1.08–1.29) or apical repair (HR 1.24, 95% CI 1.10–1.41). Simultaneous anterior repair or apical prolapse surgery also increased the need for sling revision for urinary retention.

In my experience, erosions after retropubic MUS almost always occur in the midline under the urethra. Early midline exposures are due to incomplete healing of the suburethral incision, especially in women with medical conditions that compromise tissue healing such as diabetes mellitus, history of smoking, or significant vaginal atrophy. Delayed erosions almost always occur in the midline due to thinning of the epithelium in postmenopausal women. Lateral vaginal erosions following retropubic MUS procedures are very uncommon, as there is minimal mesh material in contact with the peri-urethral vaginal epithelium. In my experience these lateral erosions are typically due to unrecognized vaginal perforations at the time of implantation or excess thinning of the peri-urethral

vaginal epithelium created by overly superficial dissection during implantation leading to early or later erosions. Vaginal erosions following transobturator MUS can occur in either the midline or can be encountered in the lateral peri-urethral area where the sling arms pass under the vaginal epithelium. The factors contributing to exposure or erosion after a transobturator MUS are similar to the mechanisms detailed above for retropubic MUS. Regardless of the type of MUS, minimal erosions may respond to office excision and improvement of the vaginal epithelium in postmenopausal women. I have found that even larger vaginal erosions can be readily treated transvaginally via outpatient surgery under intravenous sedation. I have rarely, if ever, seen repeat erosions following outpatient surgical removal of exposed mesh.

The findings of the multiple medium- and long-term studies outlined above regarding the efficacy of MUS procedures, the intra-operative complications, and the risks of subsequent re-operation for post-operative genitourinary problems are consistent with my clinical experience performing over 1000 mid-urethral sling operations. Over more than 25 years of performing surgery for stress urinary incontinence, I have found that the balance of the success of MUS operations compared to the short-term and long-term morbidity of the procedures is superior when compared to other SUI surgeries I have performed in the past (Burch retropubic suspensions, needles suspensions, and traditional suburethral sling procedures with autologous, xenograft, and synthetic materials). I agree with the 2014 joint AUGS and SUFU position statement that the MUS procedure is "probably

the most important advancement in the treatment of stress urinary incontinence in the last 50 years".

CLINICAL GUIDELINES AND POSITION STATEMENTS FROM NATIONAL AND INTERNATIONAL MEDICAL SOCIETIES AND TASK FORCES

American College of Obstetricians and Gynecologists (ACOG) and American Urogynecologic Society (AUGS)

In November 2015, the ACOG and AUGS published their latest *Practice Bulletin on Urinary Incontinence in Women, Number 155.* ACOG/AUGS *Practice Bulletins* are the premier postgraduate educational resource offered to over 35,000 Obstetricians and Gynecologists in the United States. The publications are written with the assistance of expert subspecialists (for the current *Practice Bulletin*, Dr. Kimberly Kenton and Dr. Scott Smilen) and undergo rigorous scrutiny and revisions by ACOG physicians and staff typically over a more than a 12-month period. The 2015 *Practice Bulletin on Urinary Incontinence in Women* states,

> "Synthetic mid-urethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women. Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic MUS. For these reasons, midurethral synthetic mesh slings

have become the primary surgical treatment for stress urinary incontinence in women."

AUGS & Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence

In January 2014, the AUGS and SUFU boards of directors approved those organizations' Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence. In that statement, the organizations concluded: "The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improve the quality of life for millions of women." The organizations also noted that "[a] broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI," and observed that "[t]here are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature." They also noted that "[t]he polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly." I agree with these statements in the AUGS & SUFU position statement.

National Institute for Health and Care Excellence (NICE) Statement

NICE issued its Clinical Guideline 171 titled "Urinary incontinence: The management of urinary incontinence in women," in September 2013. That guideline advises surgeons that, when offering patients a synthetic midurethral mesh procedure, they should "use procedures and devices for which there is current high quality evidence of efficacy and safety." The guideline then specifically identifies the Ethicon TVT and TVT-O slings—among others—as devices that meet those criteria.

International Continence Society (ICS)

The Publications & Communications Committee of the International Continence Society prepared an ICS Fact Sheet providing "A Background to Urinary and Faecal Incontinence" in July 2013. In that fact sheet's discussion of SUI treatment, the committee noted: "Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands."

American Urological Association (AUA) Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence

In November 2011, the Board of Directors of the AUA issued the AUA's Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence. In that statement, the AUA observed: "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic

polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries." They also noted that advantages of synthetic mesh sling surgery "include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction." They also noted that "[i]t is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI."

Governmental Organizations and Clinical Task Forces

On March 27, 2013 the **Food and Drug Administration (FDA)** published its updated statement regarding the use of trans-vaginally placed synthetic mesh when used as a MUS. In "Considerations about Surgical Mesh for SUI" the FDA stated: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year."

MY EXPERIENCE WITH MID-URETHRAL SLING PROCEDURES

During the 1980s and 1990s, my operations of choice for stress incontinence were the Burch colposuspension in women with urethral hypermobility without intrinsic sphincter deficiency, a pubourethral sling procedure using allografts, xenografts, or synthetic materials in women with urethral hypermobility and ISD, or a bulking agent in patients with ISD without hypermobility. When Ulmsten initially

reported the results of his retropubic TVT procedure, I was extremely skeptical given the significant differences between the TVT and my traditional incontinence operations—specifically the mid-urethral positioning of the sling and lack of attachment of the distal ends to an anchoring tissue. Once the data from the multi-center study in the United Kingdom comparing the results of the TVT MUS versus a Burch operation reported equal efficacy and faster post-operative recuperation without a significant increase in complications in the TVT group, I gradually began to adopt the technique into my practice. For over a decade I have performed a MUS procedure in all but a select few patients, primarily those with contra-indications to the placement of suburethral synthetic mesh. As opposed to the Burch colposuspension, I have found relatively equivalent success rates for the retropubic MUS procedure in women with or without intrinsic sphincter deficiency. I also have seen that the likelihood of recurrent SUI over time is less following a MUS procedure compared to a Burch operation. Over time I encountered more women with recurrent SUI and urethral hypermobility after I had performed a Burch procedure than in similar patients where I have performed a MUS. My patients' post-operative pain, recuperation time, the risk of post-operative voiding dysfunction or the need for further surgical intervention due to voiding problems or sling erosion is substantially less after a MUS procedure when compared to my patients following a traditional pubovaginal sling procedure with multiple sling materials. While I perform the TVT-O operation when indicated, I prefer the retropubic approach.

Over more than a decade, I have performed over 1000 MUS operations in women from age 28 to nearly 90. Patients almost never require analgesia other

than over-the-counter medications, and they are often amazed that their incontinence has been resolved with a relatively minor procedure. I have never experienced a neurologic, bowel, or vascular injury, and have only had 3 immediately recognized bladder perforations that were easily corrected and without sequelae. Only one of my patients has experienced incomplete healing/erosion of the vaginal incision and one patient developed a late bladder erosion. Both responded to outpatient surgical treatment. I have never encountered scarring, contraction, migration, long-term pain or dyspareunia, or urgency/urge incontinence that has necessitated surgical intervention.

As a tertiary referral center, I have re-operated on women following prior MUS procedures, and have never observed degradation of the mesh material. Plaintiffs' experts have suggested that the polypropylene mesh used in the Ethicon retropubic TVT or TVT-O degrades and loses structural integrity based on scanning electron microscope (SEM) or other such laboratory findings of explanted mesh. However, I have not observed clinically relevant mesh changes or degradation during explantation of Ethicon mesh slings. It is important to note that significant dissection of the mesh and/or surrounding tissue is required during explantation even within 1–2 weeks post-operatively when tissue incorporation has already occurred. The use of sharp dissection during removal will clearly affect the microscopic appearance of the explanted material. Since no comparative microscopic studies can be performed of mesh materials resected en bloc with the urethra and without instrument contact of the mesh in symptomatic or asymptomatic women, no clinically relevant conclusions can be made regarding

changes in the microscopic appearance of the explanted mesh and the relationship to any symptoms. While other in vitro studies of non-implanted mesh have suggested that clamping/crushing the mesh or elongation of the tape beyond 5% of its original length alters the mesh fibers, these in vitro changes are produced when handling of the mesh deviates from the recommended care of the mesh product. Intra-operative clamping of the mesh during placement or stretching it to adjust tensioning once the plastic sheaths are removed deviates from the recommended care of the product. Thus, one cannot draw clinically relevant conclusions based on studies that rely on mishandling of mesh products.

I agree with the authors of the 2014 SGS review. "When choosing between surgical procedures, any surgeon must weigh the presumed benefits with the potential risks and adverse events of these procedures. Balancing those against a specific patient's goals and desires is an important consideration .... Additionally, surgeons should evaluate their own personal success and complication rates with the procedures and products they use, as these may differ from published rates." My experience has confirmed that a minimally invasive MUS is the preferred option for treating stress incontinence. It is the "gold standard" for surgical treatment of stress urinary incontinence, and I agree with the position statements, practice guidelines and analyses by AUGS, AUA, SUFU, SGS, ICS, NICE and IUGA which recognize MUS procedures as a first-line option for women undergoing incontinence surgery. It is as effective or more effective than other surgeries and has less overall morbidity.

IFU & PROFESSIONAL EDUCATION OPPORTUNITIES

The purpose of the IFU is not to provide a complete medical education to the physician about how to perform a mid-urethral sling procedure and/or the properties and risks of using a synthetic material. The initial IFU clearly states "This package insert ... is **not a comprehensive reference** to the surgical technique for correcting Stress Urinary Incontinence. The device should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence and specifically trained in implanting GYNECARE TVT device". (ETH.MESH.02340504-67.) It also clearly states "failure to properly follow instructions may result in improper functioning of the device and lead to injury". The IFU also emphasized "these **instructions are recommended for general use** of the device. **Variations in use may occur in specific procedures due to individual technique and anatomy**". Tensioning of the tape is also described in the IFU using the criteria of near resolution of the patient's stress incontinence during a cough stress test performed intra-operatively. Multiple suggestions and warnings are included throughout the IFU to help the surgeon avoid complications such as bladder perforation and/or mechanical damage to the mesh. "Via use of the Foley catheter and the rigid catheter guide, the urethra and bladder are moved contralaterally to the side of the needle passage." Further instructions caution the surgeon to "not contact the PROLENE Mesh with any staples, clips or clamps, as mechanical damage to the mesh may occur" and that "a blunt instrument (scissors, forceps or Kelly

clamp) should be placed between the urethra and the tape during removal of the plastic sheaths." In my experience observing other surgeons in my hospital while performing a TVT procedure, few use the catheter guide to displace the bladder. I have seen other surgeons clamp across the suburethral portion of the mesh tape to facilitate visualization of the graft for positioning or tensioning. Subsequent problems related to technical deviations from the IFU are not Ethicon's responsibility.

Procedure-specific adverse events are also listed, including **injury** to structures in the pelvis, temporary or permanent lower urinary tract **obstruction**, and **foreign body reaction** that "could result in **extrusion, erosion, fistula formation and inflammation**". Notably, mesh exposure or erosion is the only unique risk with the MUS procedure versus the Burch operation that uses sutures to stabilize the urethra; in addition, material exposure or erosion has been previously described in the literature following pubovaginal slings performed with either biologic materials and synthetic mesh. As discussed earlier, wound complications also occur frequently during other stress incontinence surgeries. The sequelae or adverse events associated with using synthetic mesh materials in pelvic reconstructive surgery—either as MUS incontinence kits or for pelvic prolapse—is one of the most basic tenets of reconstructive surgery. It is discussed with medical students, residents and fellows in FPMRS on a daily basis in the OR, presented at national medical meetings, and published in the peer-reviewed and non-peer-reviewed literature. In my opinion, the IFU provides adequate information on the

device including its use and potential risks for surgeons who are trained and experienced in stress incontinence surgery and the use of synthetic mesh materials.

Multiple educational opportunities, including monographs, videos, and preceptorships were available for physicians to learn and/or improve their techniques, and experienced MUS surgeons typically do not encounter the same degree of problems as the novice surgeon. The educational opportunities address, among other things, use of the device, potential risks, and the management of complications. It is incumbent on the surgeon to honestly assess his knowledge of synthetic materials, understanding of the technique and pitfalls of a new procedure, and determine whether he is sufficiently experienced and skilled to perform the new operation. If not, education is required prior to embarking on the new surgical procedure. While all competent surgeons learn by operating and will continually modify their technique based on intra-operative findings and post-operative results, those surgeons performing pelvic reconstructive surgery understand it is different than extirpative surgery; the raw materials (i.e., the human tissue) we work with are rarely optimal quality. Residency and fellowship training would not be required, if surgery could be performed by simply reading an IFU. A surgeon should NOT rely on a medical device representative to teach him about a new material or "to walk him through" a new procedure. Ethicon is not responsible for credentialing surgeons; hospitals are designated that responsibility. I have extensive experience in credentialing FPMRS programs nationally, and the responsibility of credentialing lies with the surgeon, his or her hospital/university, and the respective boards for which the surgeon chooses to sit for certification status.

ETHICON-DEVELOPED LITERATURE REGARDING PATIENT BROCHURE

The purpose of a patient information brochure is to provide medical information about a condition, diagnostic testing, or therapeutic option using common terminology that can be understood by a non-medical individual. Since physicians may not always agree with all the information in a brochure, especially as it pertains to an individual patient, some physicians elect not to provide industry-developed brochures to their patients. The patient brochure provides basic information that is used to enhance subsequent discussions between the patient and her physician. **It is not** designed to be an all-encompassing dissertation of the medical issue or a substitute for individual physician counseling or physician-obtained informed consent. A patient brochure is an educational guideline, whether it is written by an individual physician for his patients, developed by a national organization such as the American Congress of Obstetricians and Gynecologists (ACOG), the American Urogynecologic Society (AUGS) or the NIH, or produced by a medical device company like Ethicon. This concept is illustrated by examining the patient fact sheet on "Hysterectomy" and "Surgery for Stress Incontinence" created by ACOG and published on their website (http://www.acog.org/Patients; FAQ008 Hysterectomy and FAQ166 Surgery for Stress Incontinence).

No patient education brochure includes an exhaustive list of surgical risks because the discussion of surgical risks and benefits must be tailored to an individual patient based on their current problems and comfort level in assuming

surgical risks. All hospitals require that a patient sign a separate informed consent document (not just a patient brochure) indicating she understands the indications for the procedure, benefits, alternative treatment options, and anesthetic and surgical risks. The surgeon must also sign the document confirming that he has discussed these specific issues with his patient. The patient brochure does not replace informed consent documents or the consenting process.

SUMMARY OPINIONS IN RESPONSE TO CONTENTIONS BY PLAINTIFFS' EXPERTS

Based on my discussions above and my education, my review of the literature and records, and my extensive clinical experience performing surgery for stress incontinence using all of the previously discussed procedures as well as multiple types of sutures, biologic materials and synthetic meshes (including the polypropylene mesh Ethicon employs in its TVT and TVT-O surgical kits), I disagree with plaintiffs' experts' contentions that 1) polypropylene is not a suitable material for implantation in SUI treatment; 2) the TVT mesh is cytotoxic, carcinogenic, or degrades leading to multiple post-operative, long-term clinical symptoms; 3) Ethicon's MUS mesh is heavyweight, small-pore, and contracts; 4) the TVT MUS procedure has design flaws that make it a blind procedure and should have been designed differently with an alternative mesh; 5) there is no long-term data to supporting the safety and efficacy of MUS procedures versus other SUI surgical procedures; and 6) Ethicon did not provide adequate information to physicians and patients regarding the risk of MUS procedures and mesh. The literature, guidelines,

meta-analyses and position statements by numerous professional organizations and my clinical experience do not support such opinions by plaintiffs' experts.

1. ETHICON MUS POLYPROPYLENE MESH IS SUITABLE FOR IMPLANTATION

Plaintiffs' experts have claimed that polypropylene is "not suitable for its intended application as a permanent implant for SUI" due to its biomechanical and chemical properties, Ethicon's failure to "modify/change the mesh," its failure to disclose to physicians that the material is "unsuitable" for MUS, that the polypropylene MSDS "warned against the use of the mesh in a permanently implanted device," and did not inform physicians that the mesh is cytotoxic. Those opinions are based on irrelevant and inaccurately characterized in vitro experiments, and fail to account for the extensive data in the literature regarding the clinical safety and efficacy of Ethicon's polypropylene mesh over decades in the field of general surgery and over 15 years in TVT and TVT-O procedures. As previously noted in my discussion of my clinical experience with over 1000 polypropylene mesh procedures, I have not experienced any degradation of the material over time, fraying, particle loss or clinical impact from particle loss or other distortions/disruptions of the material when handled appropriately at the time of implantation or when explanted from a patient. After the first several weeks, once tissue incorporation has occurred, the mesh position cannot migrate inferiorly or superiorly along the urethra due to tissue adherence in the suburethral area and tissue tunnels. This is in contrast to other microporous mesh where tissue incorporation does not occur. The clinical literature does not demonstrate these

changes in the mesh material, and the long-term data with Ethicon MUS are in contradiction with these plaintiff's experts' theories or supposed phenomenon.

2. ETHICON MUS POLYPROPYLENE MESH DOES NOT DEGRADE AND IS NOT CYTOTOXIC OR CARCINOGENIC

Plaintiffs' experts also opine that the design of the polypropylene macroporous mesh—whether laser cut or machine cut—creates a significant patient risk and causes untoward events due to its cytotoxicity, degradation or particle loss, and changes in porosity after implantation. In support of the opinion that the Ethicon MUS mesh degrades, plaintiffs' experts rely on the 2010 **Clavé** article in which explanted mesh samples were examined by histologic, chemical and scanning electron microscopic analysis. Clavé analyzed 32 out of 100 samples, which was less than 1/3 of the overall cohort. The authors did not describe why only some of the specimens were analyzed. Their chemical analysis did not indicate degradation of mesh. While explanted mesh specimens showed surface cracking of the mesh fibers, it is more likely than not that these changes are secondary to the dissection required for removal of the mesh, and/or processing of the specimen for histologic and scanning electron microscopic analysis or improper handling of the mesh during implantation. The Clavé study, however, does not account for handling or alteration of the mesh specimen during implantation, explanation or specimen processing. Since mesh has not been explanted from asymptomatic patients, it is impossible to conclude that any detectable surfaces changes are responsible for a patient's complaints following mesh implantation.

Plaintiffs' experts have hypothesized that mesh degradation is due to subclinical infection of the mesh material and the impact of local tissue factors such as peroxide that is damaging to the mesh. They support this opinion based on changes seen in Clavé's work. Plaintiffs' experts also state that polypropylene fibers are susceptible to oxidization and degradation by peroxide, and that peroxide is produced by vaginal flora, thus leading to material degradation. I disagree with this opinion. As detailed elsewhere in this report, any explanted material, especially mesh that has been removed for erosion, is subject to alterations and damage simply in the explant process or because it has eroded and been exposed to the vaginal environment. In 2008 **Woodruff** investigated several materials including polypropylene, cadaveric fascia and dermis, porcine dermis and autologous fascia, explanted for reasons other than material erosion. No degradation was seen in the polypropylene specimens, whereas the biologic materials including autologous fascia showed evidence of degradation. Woodruff's findings are consistent with my own clinical experience with slings derived from multiple biologic and synthetic materials. I have encountered complete autolysis and degradation of all non-autologous biologic materials used as slings, even when no erosion occurred. This degradation has manifested clinically by recurrent stress incontinence and urethral hypermobility. I have not encountered mesh degradation in explanted MUS materials, nor have I seen recurrent urethral hypermobility develop over time due to loss of the synthetic mesh material from degradation in patients I have followed for years.

Plaintiffs' experts have also opined that women with implanted MUS experience "subclinical infections" which account for mesh degradation, mesh scarring, future mesh erosion and mesh related pain. They support this theory based on a small study by **Wang** (2008) showing increased immunogenic response on immune-histochemical analysis of peri-urethral and vaginal tissue excised due to persistent urgency complaints in women after MUS procedure. I disagree with this opinion. The clinical criteria for "subclinical infection" require the presence of an infectious agent (bacteria or viral) that Wang did not demonstrate. Although Wang published his initial report in 2008, neither he nor his coauthors have published any additional work supporting his immunogenic hypothesis. While bacteria may be found in mesh material that has eroded into the vagina, urethra or bladder where it comes in contact with bacteria, once the eroded material is removed and the vaginal epithelium heals, the clinical infection has resolved. In the absence of eroded mesh, there is no scientific or clinical data to support this assertion regarding the continued presence of a "subclinical infection" causing mesh degradation and persistent symptoms. **Falconer** (2001) published one of the few studies to assess the peri-urethral tissue environment after MUS placement in the absence of mesh erosion. He obtained punch biopsies 6–8 mm lateral to the urethral opening and 10 mm deep in asymptomatic patients 2 years after MUS with polypropylene and Mersilene mesh and compared the tissue to controls to determine the inflammatory response based on changes in collagen. Minimal inflammatory response was seen on histologic sections from the polypropylene patients compared to controls and no changes in total collagen concentration or collagen extractability was seen between

the 2 groups. This is one of the few studies to examine tissue changes in asymptomatic patients. Ultimately, if subclinical infections and mesh degradation occurred as plaintiffs' experts propose, the failure rate of MUS would be considerably higher and significantly increase over time as the material deteriorated. This is not reported in the medical literature nor have I encountered it during my personal clinical experience with over 1000 MUS and over 4,000 MUS performed by my practice.

CARCINOGENESIS

Plaintiffs' experts have also alleged that the polypropylene mesh Ethicon employs in its MUS is carcinogenic and that patients have a life-time risk of developing cancer due to the implanted mesh. There is simply no credible scientific evidence to support such an opinion. Evaluation of the oncogenic potential of synthetic materials has been performed in animal models including mice and rats. While flat discs of raw polypropylene materials with smooth surfaces have been associated with the development of tumors in animals, porous materials do not show the same tumorigenic potential. **Witherspoon** (2004) implanted various hernia mesh materials in mice, but did not find any cancer (sarcoma) at implantation site for polypropylene mesh. Even if polypropylene mesh materials had shown tumorigenic potential in animal models, it is unclear that this carcinogenic potential can be translated to humans. Per Dr. David Williams, a researcher and Professor of Regenerative Medicine at Wake Forest University, "studies on biomaterial-related tumors in animals have no relevance to clinical performance in humans" (2014). Only 5 cases reported in the literature describe

any possible association between mesh and cancer. In two patients with chronically infected abdominal wall hernia, "bridged polyester meshes" (not polypropylene) were found to have associated squamous cell carcinoma in the abdominal wall at 6 and 24 years following implantation (**Birolini** 2014). **Kwon** (2012) reported an inflammatory myofibroblastic tumor in the bladder of a woman with neurofibromatosis and a prior retropubic polypropylene mesh sling. However, her bladder tumor is much more likely to be related to her underlying systemic disease and its effect on her immune system rather than her sling material. **Linder** (2016) reported two cases of cancer following 2,474 polypropylene MUS procedures over a ten-year period; one vaginal melanoma and one Stage I granulosa cell ovarian cancer. The authors concluded that these two cancers are "unlikely to be secondary to foreign body reaction from the implanted material." Given the extensive experience with polypropylene material in humans with billions of polypropylene sutures used over the past 40 years, tens of millions of hernia mesh patches implanted over the past 30 years, and over 3 million MUS procedures performed in nearly 20 years without reports of subsequent cancers, plaintiffs' experts' opinions regarding the ongoing risk of cancer in women after MUS procedure has no scientific basis.

I agree with the opinions stated by **Moalli** (2014) and colleagues regarding the controversy over implanted mesh. "The host response to an implanted material is an unavoidable consequence associated with its use, and the end outcome of biomaterial implantation may depend upon local or systemic factors including the site of implantation, quality of the tissue at the implantation site and patient

characteristics.... It is shortsighted and premature to assume that inflammation related to the implantation of a biomaterial will be associated with poor health outcomes." Furthermore, I absolutely agree with their statement "publications derived from a skewed interpretation of the literature and not solid evidence based on scientific data can lead to baseless damaging media hype and unscrupulous jury awards. It would be a tragedy for women worldwide if nonscientifically based articles regarding the potential hazards of polypropylene incited a spiraling course for the best (highest success rate and minimal morbidity) surgical procedure developed to date for stress urinary incontinence ...."

3. CHANGES IN ETHICON MESH POROSITY AND MESH CONTRACTION

Plaintiffs' experts allege that the design of Ethicon's MUS mesh tapes leads to changes in mesh porosity after implantation that results in contraction and scarring of the mesh. They support their opinion with in vitro laboratory studies using tensiometers to evaluate mesh appearance and porosity after stretching. However, in vitro assessments of mesh behavior under more than 5% tension or stretch are not clinically relevant. In properly performed MUS procedures, the sling is positioned with the overlying plastic sheaths in place to avoid stretching of the mesh material, and minimal, if any, traction is applied to the mesh during proper implantation. During the initial 2-3 weeks after implantation required for ingrowth of the tissue into the mesh material, minimal, if any, movement or displacement of the suburethral tissue occurs. This prevents traction on the implanted mesh. Since clinically the mesh undergoes minimal, if any, traction during and after

implantation, no clinically relevant distortion of the mesh pores occurs. Thus, plaintiffs' experts' contention that distortion of the mesh pores ultimately triggers increased scarring and bridging is simply not observed in the clinical setting following a properly performed MUS operation. Once ingrowth has been completed, stretching of the implanted mesh is simply not a clinical reality.

The plaintiffs' experts also support their opinions regarding changes in mesh porosity and scar bridging based on studies of explanted mesh specimens. However, as previously discussed, any changes in mesh architecture in explanted specimens cannot be conclusively attributed to the mesh itself versus changes that are created during the implantation and explantation surgery and/or the specimen processing.

4. ALLEGED DESIGN PROBLEMS

BLIND PROCEDURE

Plaintiffs' experts also contend that the Ethicon mid-urethral sling procedures are designed as "blind procedures" implying an associated increase in patient morbidity. All surgeons perform procedures using anatomic landmarks that are visualized and/or palpated during surgery. Given the nature of gynecologic care and surgery, many aspects of our clinical evaluations and surgical treatments rely heavily on palpation. The uterus and ovaries cannot be directly visualized in the office by an examiner. Thus, every pelvic exam to evaluate these structures in the office requires palpation transvaginally without actual visualization, i.e., it is a "blind" examination. Gynecologists perform thousands of these "blind"

examinations during their careers. Gynecologic procedures that assess the endometrium and endometrial cavity (endometrial biopsy or D&C) require passing an instrument through the cervix into the uterus "blindly" by palpation. For decades laparoscopic procedures have been performed by "blindly" inserting a Veress needle through the umbilicus into the abdominal cavity by palpation to insufflate the abdominal cavity prior to inserting larger trocars with cannula. Every obstetrician who assesses a woman's progress in labor by determining cervical dilation performs the examination "blindly" by palpation of the cervix. Even urethral catheterization is performed "blindly" by palpation as the catheter is inserted through the urethra and into the bladder. Thus, the hallmark of an obstetrician gynecologist is the ability to assess the pelvic anatomy and structures by palpation using established anatomic landmarks and techniques.

Prior to attempting a MUS operation, a surgeon must understand the anatomy and associated bony and surgical landmarks in the surgical field as well as the location of structures to avoid such as major vessels and nerves. The design of the MUS technique protects the bladder and urethra by using a stylet in the Foley catheter to deflect these structures away during passage of the trocar. Passage of the trocar is accomplished using bony landmarks and correct orientation of the trocar. A knowledgeable and experienced surgeon understands these surgical principles and can pass the trocar by palpation with rare untoward events.

ALTERNATIVE MESH MATERIALS

There are no practical and technically feasible alternative mesh designs that would completely prevent, or even reduce, the risk of complications such as dyspareunia, post-operative hematoma, worsening urge incontinence, or sling exposure. Plaintiffs' experts sometimes opine that other mesh materials such as UltraPro, Vypro, or Gynemesh PS should have been chosen since these materials are lighter weight and/or partially absorbable. Theoretically, a MUS mesh composed of permanent and absorbable fibers might reduce the risk of mesh-related problems after MUS. Ethicon investigated whether a partially absorbable mesh would reduce mesh complications when it developed the TVTO-PA product composed of UltraPro mesh (polypropylene and Monocryl) (ETH.MESH.09922570-78). However, the TVTO-PA product (UltraPro) was found to function poorly in cadaveric trials. The absorbable Monocryl component appeared to cause the sling to "stick" to the sheath requiring excess traction on the mesh during attempts at sheath removal. This excess traction resulted in unacceptable stretching of the mid-portion of the sling material, and UltraPro was abandoned as a MUS material. **Okulu** (2013) investigated alternative mesh materials in 144 women with stress incontinence who underwent a patch sling procedure with Vypro (Group I), Ultra-Pro (Group II) and Prolene light mesh (Group III). Although the authors reported continence rates between 85–92%, the mean surgical time was longer (55 minutes) and they provided no information regarding intra-operative complications. Post-operative complications related to the mesh and suture material were markedly higher than reported with other MUS procedures despite their attempt to preserve an optimal flap of vaginal epithelium to cover the implanted mesh. The Vypro group had a

4.3% vaginal erosion rate, 2.2% urethral erosion rate, a 6.5% suture granuloma rate, a 4.3% urine retention rate, an 8.7% incontinence rate, and a 10.9% de novo urgency rate. The UltraPro Group had a 2.1% vaginal erosion rate, a 2.1% suture granuloma rate, a 4.2% urine retention rate, a 2.1% incontinence rate, and a 4.2% de novo urgency rate. The Prolene light group had a 4.3% vaginal erosion rate, a 2.1% urethral erosion rate, a 6.4% suture granuloma rate, a 4.3% urine retention rate, an 8.5% incontinence rate, and a 8.5% de novo urgency rate. Other investigators have also concluded that a partially absorbable mesh material does not appear to reduce the risk of mesh erosion in vaginal surgery. **Milani** (2012) reported the 3-year results of Prolift+M for vaginal prolapse repair and reported a 14.8% mesh exposure rate at 3 years.

Vypro has also been evaluated in vaginal prolapse repairs and been found to have an unacceptable rate of mesh-related complications despite being partially absorbable. **Denis** (2004) reported a 9.5% mesh erosion rate at a mean follow-up of 7.9 months, with 70% of patients requiring more than one treatment for persistent mesh exposure and 10.4% requiring surgical removal of mesh in the operating room. The investigators concluded "the use of a half absorbable mesh does not seem to reduce the inflammation and could even accentuate it". **Lim** and colleagues (2007) also reported a 30% mesh erosion rate and a 22% recurrent rectocele rate at a mean of 35 months following a posterior repair augmented with Vypro mesh.

Despite an intensive review of the medical literature, the only study that I was able to find that analyzes Gynemesh PS and UltraPro for the treatment of SUI is

the Okulu 2013 study discussed above. However, Okulu's study cannot be used to conclude that Gynemesh PS or Vypro would eliminate or reduce the potential risks of MUS procedures, for the following reasons:

- The authors studied the use of these mesh materials in groups of only 48 patients. These cohorts are too small to draw any definitive comparisons about clinical efficacy and safety of these sling materials, especially when compared to the cumulative data on thousands of patients who have undergone polypropylene MUS operations.

- The slings in the study are not equivalent to Ethicon's retropubic MUS procedure. Unlike the Ethicon TVT procedures, Okulu's slings were implanted after making an inverted "A"-shaped incision in the vaginal epithelium, creating a patch of sling with polypropylene suture arms, and anchoring the suture arms to the rectus fascia. Okulu's sling procedure is not a tension-free retropubic MUS given the significant variation in technique.

- Okulu's results did not indicate a reduction—much less elimination—of MUS risks such as vaginal exposure: Okulu noted vaginal exposure rates of 4.25% and 2.08% for Prolene Soft and UltraPro, respectively, which is higher than reported for retropubic MUS operations in **Novara's** 2008 meta-analysis. He found several studies of retropubic MUS with up to 24-month follow-up that demonstrated vaginal exposure rates between 1–2%.

Even if a meaningful comparison could be drawn from the results of the Okulu study, which it cannot, the study was not published until 2013 and would not reflect evidence of alternative designs that were available for patients who received a retropubic MUS that was sold before 2013.

Thus, while plaintiffs' experts opine that Ethicon should have employed alternative mesh materials that are partially absorbable, have larger pores, or are lighter-weight to reduce the risk of mesh-related complications, clinical evidence does not support that recommendation and does not show that those alternative meshes were technically feasible alternative designs for the TVT device.

Furthermore, to my knowledge, the FDA has never cleared UltraPro, Vypro, or Gynemesh PS mesh for treatment of SUI. Rather, according to information on the FDA's website, Vypro is cleared for repair of hernia or other fascial defects[1], UltraPro mesh is cleared for repair of hernias and other abdominal fascial deficiencies[2], and Gynemesh PS is cleared for the repair of hernia or other fascial defects and the treatment of pelvic organ prolapse through an abdominal approach[3].

LASER CUT MESH

Plaintiffs' experts also sometimes offer the opinion that laser-cut mesh would have been a feasible and safer alternative design to the mechanically cut mesh used in the original Ethicon TVT device. However, no studies indicate that laser-cut mesh is safer or more effective than mechanically cut mesh. The difference between

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[1] http://www.accessdata.fda.gov/cdrh_docs/pdf/K002672.pdf.
[2] http://www.accessdata.fda.gov/cdrh_docs/pdf3/K033337.pdf.
[3] http://www.accessdata.fda.gov/cdrh_docs/pdf/K013718.pdf.

mechanically cut mesh and laser-cut mesh is simply aesthetic and based on surgeon preference for the type of mesh and the insertion trocars. No studies support plaintiffs' experts' contention that laser-cut mesh is safer than mechanically cut mesh. Studies of laser-cut mesh show that complications such as hematoma, dyspareunia, exposure, and de novo or worsening urge incontinence can still occur with laser-cut mesh. My experience using both Ethicon's mechanically cut retropubic MUS and laser-cut retropubic MUS has demonstrated no difference in the safety of the mesh based on the cutting technique. While plaintiffs' experts allege that mechanically cut mesh leads to particle loss from the edges of the mesh, I have never encountered this clinically when the mesh is handled properly during implantation. Additionally, there is no data showing mesh particles migrate to other areas of the body and/or create any adverse effects in the local tissue area.

5. LONG TERM DATA REGARDING SAFETY AND EFFICACY

Plaintiffs' experts or their counsel have contended that there is a lack of long-term data on the safety and efficacy of MUS procedures despite significant data to the contrary as discussed in this report. Furthermore, plaintiffs' experts opine that alternative traditional surgeries, such as an open retropubic Burch procedure or an autologous rectus fascia urethral sling are better alternative surgical treatment options for SUI. I strongly disagree with these statements. I have not seen plaintiffs' experts provide any data to support this opinion on their personal experience with the Burch colposuspension or rectus fascia sling they advocate. I have not seen their results published any peer-reviewed papers, nor have I seen any clinical trials they have conducted regarding the safety and efficacy of these operations.

In this report, I have detailed the extensive medical literature, clinical guidelines from multiple national and international surgical societies, and governmental organizations and task forces that support the long-term safety and efficacy of MUS procedures for the treatment of SUI. There is extensive data in the literature showing MUS procedures are as effective in the short-term and long-term, if not more so, than Burch colposuspension or autologous sling procedures. While Ethicon MUS are designed to be minimally invasive procedures that can be performed as an outpatient and without general anesthesia in many circumstances, the plaintiffs' experts opine that this provides no additional benefit to the patient compared to alternative surgeries. I disagree with this opinion. MUS procedures can be performed under local anesthesia with or without intravenous sedation. Neither Burch colposuspensions nor autologous sling procedures can be performed under local anesthesia alone. Laparoscopic Burch procedures require a general anesthesia with intubation, while open Burch procedures and autologous sling procedures are performed either similarly or under regional anesthesia. Compared to IV sedation and local anesthetic options, general anesthesia increases the operative time, recovery room time, the risk of post-operative nausea and/or vomiting, and the patient's risk of anesthetic-related complications such as aspiration, fever, atelectasis, and pneumonia. While vaginal procedures can be done under regional anesthesia, not all patients are candidates for regional anesthetic due to a history of underlying back or spinal problems, neurologic disease, or being on prophylactic anticoagulants. Patients with regional anesthesia have increased operating and recovery room time, risk of pain at the injection site, and risk of spinal

headache that can be severe enough to require a subsequent procedure for a blood patch. Both general and regional anesthetics increase the overall cost of surgery.

Another advantage of MUS procedures that the plaintiff's experts fail to consider is that MUS require less surgical dissection to complete the operation, which reduces operating room time and the operative risks associated with length of surgery. Plaintiffs' experts contend that only pelvic surgeries exceeding 2 hours' duration pose an increased risk of adverse post-operative events such as deep venous thrombosis and/or pulmonary embolism (thromboembolic events). This is inaccurate. One of the primary factors determining the risk of thromboembolic events, and thus the need for prophylaxis at the time of a gynecologic procedure, is duration of surgery more than 30 minutes (ACOG Practice Bulletin #84, 2007, 2013). The majority of MUS procedures are accomplished in less than 30 minutes, whereas Burch colposuspensions and autologous sling procedures require more dissection and longer operating time, typically exceeding 30 minutes. **Kim** (2015) examined the risk of post-operative venous thrombosis in over 1.4 million patients undergoing surgery under general anesthesia and concluded "an increase in surgical duration was directly associated with an increase in the risk for venous thromboembolism". **Barber** (2015) showed that more extensive anesthesia, more surgical dissection, and longer operative time are associated with longer hospital stays, which in turn, are also associated with a further increased risk of thromboembolic events.

Surgeries requiring larger abdominal incisions place the patient at risk of post-operative wound infections and/or hernia formation. The suprapubic incisions required for a retropubic MUS procedure are each 0.3–0.5 cm in length as opposed to 4–6 cm for either a Burch procedure or even more extensive for harvesting autologous rectus fascia for a sling procedure. Harvesting a strip of rectus fascia also creates increased tension on the resulting rectus fascia closure leading to the possibility of increased pain, incision separation, or hernia formation. If autologous fascia lata is used as the sling material, a second operative site is needed to harvest fascia lata. The donor site is at risk for post-operative complications such as pain, infection and potential orthopedic problems.

Post-operative pain is less with MUS procedures allowing the patient to return to normal activities more quickly. In my experience, the majority of women undergoing a MUS procedure do not require post-op narcotic pain medication after leaving the recovery room or they discontinue usage within 24 hours. Patients typically require narcotic analgesia for days to weeks following Burch colposuspension and autologous fascial slings.

Additional literature refuting the plaintiffs' expert opinion regarding comparative safety of MUS versus other SUI surgeries is found in the **Schimpf** 2014 SGS systematic review and meta-analysis that reported summary estimates of complications following retropubic MUS, the Burch procedure and a pubovaginal sling. In their series, the summary estimate of the prevalence of immediate post-operative complications such as hematoma and wound infections were reported as

0.88% and 0.75% for retropubic MUS, respectively; 1.4% and 7% respectively for Burch procedures; and 2.2% and 2.6% for pubovaginal sling operations, respectively.

Burch procedures and autologous sling procedures have at least the same, if not more risk of re-operation than MUS operations. While non-mesh operations avoid the small risk of re-operation for mesh erosion or extrusion (2–3%), these alternative procedures are associated with a higher rate of re-operation due to other post-operative sequelae. It has been well-established for decades that Burch colposuspension procedures are associated with a significant risk of developing or exacerbating pelvic organ prolapse within a short time interval following the index surgery. **Wiskind** (1992) found a 26.7% rate of re-operation for genital prolapse in 131 women within 5–10 years following a Burch colposuspension. **Kjolhede** (1996) reported a 29% re-operation rate for corrective prolapse surgery within 2 years after a Burch colposuspension. **Langer** (2001) evaluated the appearance of post-operative anatomic defects over 10 years in 127 women who underwent a Burch procedure. He reported 18.7% developed anatomic defects with 16.7% of the defects diagnosed by 5 years and 83.3% of defects detected by 10 years. **Demirci** (2001) detailed the late complications of a Burch procedure in a group of 220 women noting 37.3% midline or apical prolapse (8.2% cystocele, 14.5% rectocele and 16.0% enterocele). He also found a 2.7% rate of dyspareunia and 6.8% groin or suprapubic pain. While MUS procedures are associated with a 2–3% risk of re-operation for mesh erosion or extrusions, surgical correction of the mesh erosion is typically relatively straightforward, performed as an outpatient procedure under

intravenous sedation, and has a very high chance of resolving the problem. In contrast, correcting genital prolapse following a Burch procedure requires more extensive surgery with a >30% chance of recurrent prolapse despite surgical repair.

RISKS VERSUS BENEFITS

Plaintiffs' experts have opined that the risks of the Ethicon MUS procedures significantly outweigh the benefits of these procedures. They contend that the biomechanical and chemical properties of the polypropylene mesh used by Ethicon for MUS cause a host of mesh problems in vivo leading to a list of possible injuries and imply that alternative procedures such as an abdominal retropubic operation or traditional pubourethral sling procedure would not cause these injuries.

I strongly disagree with plaintiffs' experts' opinions. The literature, clinical guidelines, meta-analyses, and position statements by the Cochrane review and numerous professional organizations as well as my clinical experience do not support such an opinion. I have detailed previously the medical literature regarding complications following all surgeries for SUI. Table 2 lists the symptoms and risks specified by plaintiffs' experts as due to Ethicon's MUS mesh and compares the actual complication data in 10 RCTs of MUS versus Burch procedures and 5 RCTs of MUS versus sling trials. In reality, most of the complications listed by plaintiffs' experts are more commonly found with the traditional stress incontinence procedures where mesh is not utilized than in MUS patients.

Table 2. Comparison of complication rates by procedure for the 2014 SGS Systematic Review Group

Proposed polypropylene mesh injuries	**Retropubic MUS**	**Obturator MUS**	**Burch**	**Sling**
Recurrent stress incontinence or worsening incontinence	*	*	*	*
Wound infection	0.75%	0.74%	**7.0%**	2.6%
Rejection/erosion of materials	3.4%	4.9%	0.28%	**7.0%**
Urinary dysfunction Voiding dysfunction >6 weeks Overactive bladder symptoms	9.6% 6.9% 2.7%	7.7% 5.3% 2.4%	11.9% 4.3% 7.6%	**15.1%** 8.6% 7.5%
Injury to urinary tract (ureters, bladder, urethra) or bowel	4.35%	2.12%	**6.54%**	2.48%
Chronic dyspareunia Sexual dysfunction	**	**	**	No data
Need for additional surgery Possible multiple erosions	***	***		***
Chronic debilitating pain	No data	No data	No data	No data
Pelvic Abscess	No data	No data	No data	No data
Risk of infection	No data	No data	No data	No data

*No difference was found in subjective or objective cure rates between the MUS procedures and the Burch colposuspension or pubovaginal slings, although

subjective data from the MUS vs Sling analysis showed a trend favoring MUS. **Comparisons of 10 RCTs found no difference in QOL or sexual function outcomes between the MUS and Burch procedure. ***In 5 RCTs comparing MUS and pubovaginal slings, there was no difference between the groups regarding return to the OR for material erosion or urinary retention.

Plaintiffs' experts have alleged that the Ethicon MUS mesh is responsible for symptoms of persistent or de novo urgency and/or urge incontinence symptoms in any patient following a MUS procedure. Women with mixed urinary incontinence often undergo surgical procedures to treat the stress component of their incontinence; but surgeons are well aware that no SUI surgery is designed to alleviate urgency, frequency, and urge incontinence symptoms (OAB). Some women may experience improvement of their OAB post-operatively, which is thought to be due to correction of proximal urethral funneling. However, as discussed above in this report, persistent symptoms of OAB may be seen after any stress incontinence procedure, and in some patients OAB symptoms can be exacerbated following surgery for SUI. De novo symptoms of OAB are also reported with all surgeries for SUI. **Schimpf** and the SGS Systematic Review Group's 2014 metaanalysis found post-operative urgency was less common after retropubic MUS procedures (6.9%) than after autologous fascial slings (8.6%). De novo urgency and urge incontinence symptoms are also more prevalent after autologous sling procedures. In 2010 **Dmochowski** and colleagues published the AUA Guidelines on the Surgical Management of SUI after reviewing nearly 600 articles on efficacy and

complications of the different procedures. The prevalence of post-operative urgency and urge incontinence symptoms summarized in Table 3.

Table 3. Median Percentage of Urge Incontinence 12–23 months after SUI Surgery

Procedure	De Novo UUI (range)	Persistent UUI (range)
Burch colposuspension	8% (5–11)	17% (4–40)
Autologous fascial slings	9% (6–13)	33% (28–40)
Cadaveric fascial sling	28% (13–47)	21% (10–36)
Synthetic MUS	6% (3–10)	44% (26–63)

Clearly, the persistence, worsening, or development of post-operative OAB symptoms is not mesh dependent. There is also no scientific data to support plaintiffs' experts' allegations that subclinical infection due to the presence of mesh following MUS procedures is the underlying cause of persistent or de novo OAB symptoms post-operatively. Possible alternative explanations include persistent urinary tract infections, bladder outlet obstruction or idiopathic causes.

Table 4 provides additional data to refute the plaintiffs' experts' claims that Ethicon MUS mesh is the sole cause of post-operative complaints including pain or sexual dysfunction. It lists risks and injuries highlighted by plaintiffs' experts and compares the data on actual complication rates as outlined in the revised 2012 AUA

SUI Guidelines. The AUA data also underscores the increased risk of post-operative complications or symptoms after any type of incontinence surgery in women having concomitant prolapse procedures compared to women who undergo SUI alone operations.

Table 4. Comparison of complication rates by procedure from the revised 2012 AUA SUI Guideline

Proposed polypropylene mesh injuries	**MUS (Any Prolapse/No prolapse)**	**Burch (Any Prolapse/No prolapse)**	**Sling (Any Prolapse/No prolapse)**
Pain	3% / 1%	9% / 6%	3% / 10%
Sexual dysfunction	NR / 0%	7% / 3%	NR / 8%
Systemic - Abscess	3% / 1%	4% / 7%	NR / NR
Risk of infection	1% / NR	12% / 2%	4% / 0%

Plaintiffs' experts have alleged that Ethicon MUS mesh is the cause of any and all patients chronic post-operative pain following implantation of a MUS. I strongly disagree with this opinion. Chronic post-surgical pain is reported in 10–50% of patients following **ANY** surgical procedure with 18.3% reporting severe pain. After hysterectomy, 17% of women reported chronic pain and 12.2% report chronic pain after genito-urinary procedures (**Althaus** 2012, **Johansen** 2012). Thus, all surgeries for SUI place the patient at risk of pelvic pain and/or dyspareunia and surgeons are responsible for advising patients of these risks during their pre-

operative counseling regarding the risks and benefits of any pelvic surgery. All surgeons are also cognizant that in a small number of patients, post-operative pain may become a permanent sequel of surgery. Women with SUI or prolapse, especially postmenopausal women, often report symptoms of pre-operative pain and/or dyspareunia which places them at increased risk of post-operative pain or dyspareunia.

Similar to MUS operations, all alternative surgeries for SUI such anterior repair, Burch colposuspensions and fascial slings procedures carry the risk of short-term or permanent post-operative pain and/or dyspareunia. **Lemack** (2000) found a 29% dyspareunia rate before surgery and a 20% rate after anterior repair for SUI with or without posterior repair with 18% of women reporting worsening dyspareunia after surgical correction. Following Burch colposuspension and posterior colporrhaphy, 38% of women reported dyspareunia (**Weber** 2000). **Cavan** (2008) compared sexual function in 94 women who underwent either a Burch colposuspension or vaginal sling. Using the FSFI questionnaire, 12.2% and 63.4% of patients undergoing a Burch colposuspension reported improvement or worsening in sexual function, respectively. In the vaginal sling group 24.5% and 47.2% showed improvement or worsening sexual function, respectively. Studies regarding MUS procedures have shown improvement, no change, and worsening of sexual function after surgery. As previously noted, dyspareunia is also more common after MUS procedures in women who undergo concomitant prolapse repairs and in women with a history of prior surgery for stress incontinence or prolapse. In the TOMUS trial, a prospective RCT trial of MUS procedures, **Zyczynski**

(2012) reported 597 women who underwent either a retropubic or transobturator MUS procedure had overall improvement of dyspareunia, incontinence during coitus, and fear of coital incontinence at 2 years post-operatively. **Shah** (2005) found no difference in sexual function in 29 women after polypropylene sling. Mailed questionnaires have been used to assess sexual function in several retrospective trials. **Mazouni** (2004) found 20% of women reported impairment after surgery including 14.4% dyspareunia, while **Sentihes** (2009) assessed women after only MUS procedures with 17.3% and 12.5% complaining of sexual function deterioration after retropubic or transobturator MUS, respectively.

Pelvic surgeons are also well aware of the multiple possible causes and management of post-operative pain including dyspareunia following any pelvic surgery. The etiologies include atrophic vaginal tissue in postmenopausal women, changes in vaginal caliber and length, reduced pliability of vaginal tissues due to scar tissue, changes in innervation, exacerbation of pelvic muscle dysfunction and spasm, and sensitivity of granulation tissue formed due to mesh or suture used in surgical reconstruction. Dyspareunia following MUS procedures may be related to any of these etiologies.

Plaintiffs' experts contend that women who experience pelvic pain or dyspareunia following a MUS procedure, especially those with mesh exposure, are at risk for persistent pain even if the eroded mesh is removed. I strongly disagree with this allegation based on the medical literature and my clinical experience with removal of exposed mesh associated with pain or dyspareunia. **Kuhn** (2009)

published the results of a prospective trial of 21 women referred for mesh erosion after suburethral sling procedures using pre-op and post-op FSFI questionnaires. Following treatment of the erosion, these authors found significant improvement in the domains of pain, sexual desire, arousal, lubrication and satisfaction 3 months post-operatively. **Rigaud** (2010) reported the results of 17 women who had mesh removed for post-operative pain following either retropubic or transobturator MUS operations. Removal of the mesh resulted in >50% improvement of pain by visual analogue score in 68% of patients. The authors stated that "in most cases an abnormal tape position or excessive tape traction" was found at the time of surgery. This stated finding is consistent with my intra-operative experience in removing suburethral mesh for pain or dyspareunia after MUS slings. When removing mesh for pain, I usually discover the tape is abnormally positioned, either too distally or proximally even under the bladder, or under excess tension with restrictive scar band formation especially in the lateral peri-urethral area. One cannot attribute this abnormal finding to solely mesh contraction or scarring since that degree of contracture should also lead to concomitant voiding problems; a finding I have rarely encountered. Once I have successfully removed the eroded mesh, granulation tissue and/or restrictive scar bands, patients almost always report resolution of their symptoms. **Hou** (2014) and colleagues reported 81% of women were pain free at 6–47 months after removal of MUS mesh removal for pain. Post-operative dyspareunia due to other etiologies can be treated with alternative therapies include vaginal estrogen to improve vaginal atrophy, physical therapy to address pelvic muscle spasm and improve tissue pliability, or trigger point injections of

persistent areas of tenderness or pain. If this multimodality treatment approach is followed, I have rarely, if ever, had women complain of continued pain symptoms.

6. IFU AND PATIENT BROCHURE INFORMATION

Plaintiffs' experts have also contended that it was Ethicon's responsibility to list **all** potential surgical risks and benefits for an individual patient in the IFU and Patient Brochure for its MUS procedure. I disagree with that opinion as it is clearly impossible and unnecessary for all risks to be anticipated and outlined in company literature. The IFU and patient brochures are to aid a surgeon and a patient, respectively, but they are not a substitute for surgeon' knowledge or his clinical and surgical expertise; nor are the documents a substitute for the surgeon's responsibility to adequately counsel a patient regarding the pros and cons of different treatment options and appropriately consent her for surgery. Surgeons do not need to be re-taught in a product's IFU what they previously learned in their medical school education or their residency and fellowship training. Please see my previous discussion on IFU and Patient Brochure.

CONCLUSION

In conclusion, millions of women suffer from SUI that affects their quality of life, prevents them from participating in normal activities of daily living, and creates an economic hardship due to the direct costs of caring for their problem. Nonsurgical options are unlikely to cure the problem and require maintenance of any behavioral changes or the use of a device. Many women with SUI choose to undergo surgical treatment, as this option gives them the best chance of resolving

their incontinence. As with any operation, surgery for SUI is associated with a risk of potential complications. Traditional surgical repairs such as Burch colposuspension and pubovaginal slings result in longer hospital stays and post-operative recuperation without an improvement in surgical success rates when compared with MUS. Serious adverse events following MUS are less frequent overall when compared to more the invasive procedures. It is incumbent upon the surgeon to weigh the risks and benefits of different surgical procedures with each woman. Given the nature of surgery, some women who chose to proceed with surgery will experience a complication that may require further treatment. The fact that a patient develops one or more complications does not mean the products or devices employed in the operation were defective or accompanied by inadequate warnings for the surgeon or the patient.

Dated: 2/25/2016

Nicolette Sigrid Horbach, M.D.